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Evaluation Report ERC2014-03

Pyraflufen-ethyl

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Overview

Registration Decision for Pyraflufen-ethyl

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, has granted conditional registration for the sale and use of Nufarm Pyraflufen-ethyl Technical and NUP6D 04 Herbicide, containing the technical grade active ingredient pyraflufen-ethyl, to be used on field corn, soybeans and wheat as preseed or pre-emergence application for broadleaf weed control in Canada.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

Although the risks and value have been found acceptable when all risk reduction measures are followed, the applicant must submit additional scientific information as a condition of registration.

This Overview describes the key points of the evaluation, while the Science Evaluation section provides detailed technical information on the human health, environmental and value assessments of Nufarm Pyraflufen-ethyl Technical and NUP6D 04 Herbicide.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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[1] "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

[2] "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

What Is Pyraflufen-ethyl?

Pyraflufen-ethyl is the active ingredient in the end-use product NUP6D 04 Herbicide. It belongs to the phenylpyrazole chemical family and is a contact herbicide for control or suppression of several emerged broadleaf weeds, specifically lamb's-quarters, redroot pigweed, volunteer canola, dandelion, flixweed, wild buckwheat, kochia and stinkweed, prior to emergence of wheat (spring, durum, and winter), field corn, and soybean. As an inhibitor of protoporphyrinogen oxidase (PPO), pyraflufen-ethyl results in cell membrane destruction and necrosis. The foliage of sensitive plants turns yellow and brown with leaf burn, followed by death of the whole plant.

Pyraflufen-ethyl is classified as a Group 14 herbicide by the Weed Science Society of America and as a Group E herbicide by the Herbicide Resistance Action Committee.

Health Considerations

Can Approved Uses of Pyraflufen-ethyl Affect Human Health?

NUP6D 04 Herbicide, containing pyraflufen-ethyl, is unlikely to affect your health when used according to the proposed label directions.

Potential exposure to pyraflufen-ethyl may occur through the diet (food and water) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

In laboratory animals, the technical grade active ingredient pyraflufen-ethyl was of low acute toxicity by the oral, dermal and inhalation routes of exposure. Pyraflufen-ethyl was minimally irritating to the eyes and non-irritating to the skin, and did not elicit an allergic skin reaction. Consequently, these findings do not trigger a requirement for hazard labelling.

The end-use product NUP6D 04 Herbicide, containing pyraflufen-ethyl, was of low acute toxicity via the oral, dermal and inhalation routes of exposure. It did not cause an allergic skin reaction. It was severely irritating to the eyes and extremely irritating to the skin. Consequently, the hazard signal words "DANGER – CORROSIVE TO EYES AND SKIN" are required on the label.

In laboratory animals given daily oral doses of pyraflufen-ethyl over a long period of time, effects on the liver, kidney, and blood forming system were observed. Pyraflufen-ethyl did not cause cancer in the rat and did not damage genetic material. It caused an increase in the incidence of liver tumours in the mouse. Pyraflufen-ethyl affected immune response in male rats at a very high dose. Abortions were observed in pregnant rabbits at a dose causing death in the mothers. When pyraflufen-ethyl was given to pregnant or nursing rats, no effects on the developing fetus or juvenile animal were observed at doses that were toxic to the mother, indicating that the young were not more sensitive to pyraflufen-ethyl than the adult animal. Pyraflufen-ethyl did not affect the reproductive system.

The risk assessment protects against the effects of pyraflufen-ethyl by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and drinking water are not of health concern.

Aggregate dietary intake estimates (food plus drinking water) revealed that the general population and children 1-2 years old, the subpopulation that would ingest the most pyraflufen-ethyl relative to body weight, are expected to be exposed to less than 1% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from pyraflufen-ethyl is not of health concern for all population subgroups.

The lifetime cancer risk from the use of pyraflufen-ethyl on field corn, soybeans and wheat is not of health concern.

Animal studies revealed no acute health effects. Consequently, a single dose of pyraflufen-ethyl is not likely to cause acute health effects in the general population (including infants and children).

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout the United States, including representative Canadian growing regions, using pyraflufen-ethyl on field corn, soybeans and wheat are acceptable. The MRLs for this active ingredient can be found in the Science Evaluation section of this Evaluation Document.

Occupational Risks from Handling NUP6D 04 Herbicide

Occupational risks are not of concern when NUP6D 04 Herbicide is used according to the label directions, which include protective measures.

Farmers and custom applicators that mix, load or apply NUP6D 04 Herbicide can come in direct contact with pyraflufen-ethyl residues on the skin. Therefore, the label specifies that anyone mixing/loading and applying NUP6D 04 Herbicide must wear long pants, a long-sleeved shirt, socks and shoes. In addition, workers mixing and loading must wear chemical resistant gloves, and goggles or a face shield. The label also requires that workers do not enter treated fields for 12 hours after application. Taking into consideration these label statements, the number of applications and the expectation of the exposure period for handlers and workers, health risk to these individuals are not of concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Pyraflufen-ethyl Is Introduced Into the Environment?

Pyraflufen-ethyl may pose a risk to beneficial arthropods, terrestrial plants and aquatic organisms, such as amphibians and algae.

Pyraflufen-ethyl enters the environment when it is used as an herbicide for control of weeds on a variety of crops. Spray drift from ground applications and run-off from the site of application can enter non-target terrestrial and aquatic habitats. In both soil and water, pyraflufen-ethyl transforms quickly and is not expected to bioaccumulate. The major transformation products formed in soil and/or water are non-persistent to persistent. The major transformation product E-1 does not bioconcentrate in fish and further information is to be submitted regarding bioconcentration of the transformation product E-3. Although pyraflufen-ethyl is not likely to leach to groundwater, some of the major transformation products have the potential to leach through the soil profile and enter groundwater.

Overall, pyraflufen-ethyl and its major transformation products present a negligible risk to pollinators, birds, small mammals and fish (freshwater and marine). However, pyraflufen-ethyl may affect beneficial arthropods, terrestrial plants, freshwater algae and amphibians.

To reduce exposure of terrestrial plants and aquatic organisms, spray buffer zones between sites of application and non-target areas are required. Precautionary label statements will be used to inform users of all risks to the environment and to help reduce the potential for surface runoff.

Value Considerations

What is the Value of NUP6D 04 Herbicide?

NUP6D 04 Herbicide may be applied prior to seeding or emergence of wheat (spring, durum, winter), field corn, and soybean at a rate of 4.5 g a.i./ha in combination with a non-ionic surfactant (NIS) at 0.25% v/v to combat infestations of emerged broadleaf weeds; specifically to control lamb's-quarters and redroot pigweed and to suppress volunteer canola, dandelion, flixweed, wild buckwheat, kochia and stinkweed. NUP6D 04 Herbicide may be applied once per growing season by ground application equipment.

There are several Group 14 herbicides registered for application prior to crop emergence for control of emerged weeds, but none belong to the phenylpyrazole chemical family. The value of NUP6D 04 Herbicide relates to its potential contribution to herbicide resistance management as well as providing growers an additional weed control option within the Group 14 mode of action category.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of NUP6D 04 Herbicide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with pyraflufen-ethyl on the skin or through inhalation of spray mists, anyone mixing, loading and applying NUP6D 04 Herbicide must wear long pants, a long-sleeved shirt, socks and shoes. In addition, workers mixing and loading must wear chemical resistant gloves, and goggles or a face shield. Standard label statements to protect against drift during application were also added to the label.

Environment

- Precautionary statements to protect non-target terrestrial and aquatic organisms and no-spray buffer zones for non-target terrestrial and aquatic habitats are required.
- To reduce the potential for runoff of pyraflufen-ethyl to adjacent aquatic habitats, precautionary statements for sites with characteristics that may be conducive to runoff and when heavy rain is forecasted are required.
- To reduce the potential build-up of soil transformation products, precautionary label statements will be used.

What Additional Scientific Information Is Being Requested?

Although the risks and value have been found acceptable when all risk-reduction measures are followed, the applicant must submit additional scientific information as a condition of registration. More details are presented in the Science Evaluation section of this Evaluation Report or in the Section 12 Notice associated with these conditional registrations. The applicant must submit the following information within the time frames indicated.

Environment

A bioaccumulation study is being requested for E-3, a transformation product of pyraflufen-ethyl.

Other Information

As these conditional registrations relate to a decision on which the public must be consulted[3] the PMRA will publish a consultation document when there is a proposed decision on applications to convert the conditional registrations to full registrations or on applications to renew the conditional registrations, whichever occurs first.

The test data cited in this Evaluation Report (in other words, the test data relevant in supporting the registration decision) will be made available for public inspection when the decision is made to convert the conditional registrations to full registrations or to renew the conditional registrations (following public consultation). If more information is required, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (pmra.infoserv@hc-sc.gc.ca).

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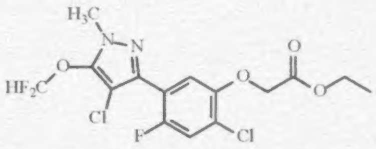
[3] As per subsection 28(1) of the *Pest Control Products Act.*

Science Evaluation

Pyraflufen-ethyl

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Pyraflufen-ethyl
Function	Herbicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	Ethyl [2-chloro-5-(4-chloro-5-difluoromethoxy-1-methylpyrazol-3-yl)-4-fluorophenoxy]acetate
2. Chemical Abstracts Service (CAS)	Ethyl 2-[2-chloro-5-[4-chloro-5-(difluoromethoxy)-1-methyl-1*H*-pyrazol-3-yl]-4-fluorophenoxy]acetate
CAS number	129630-19-9
Molecular formula	$C_{15}H_{13}Cl_2F_3N_2O_4$
Molecular weight	413.18
Structural formula	
Purity of the active ingredient	97.5%

1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product

Technical Product—Pyraflufen-ethyl Technical

Property	Result
Colour and physical state	Cream solid
Odour	No detectable odour
Melting range	126.4–127.2°C
Boiling point or range	N/A
Relative density at 24°C	1.565
Vapour pressure at 25°C	1.6×10^{-8} Pa
Henry's law constant at 20°C	7.95E-10 atm m^3/mole

Ultraviolet (UV)-visible spectrum	pH λ_{max} ε (Lmol^{-1}cm^{-1}) acidic 203 27400 243 13000 292 5800 neutral 203 28700 243 12800 291 5900 basic 207 30700 243 12100 294 5700 No absorbance at $\lambda > 350$ nm
Solubility in water at 20°C	0.082 mg/L
Solubility in organic solvents at 20°C (g/100 mL)	Solvent Solubility (g/L) n-heptane 0.234 methanol 7.39 *p*-xylene 41.7-43.5 1,2-dichloroethane 100-111 ethyl acetate 105-111 acetone 167-182
n-Octanol-water partition coefficient (K_{ow})	Log $K_{ow} = 3.49$
Dissociation constant (pK_a)	No dissociation
Stability (temperature, metal)	The product is stable at normal and elevated (54°C) temperatures, and is stable to iron and aluminum at ambient temperature (for a two-week period).

End-Use Product— NUP6D 04 Herbicide

Property	Result
Colour	Slightly yellow to brown
Odour	Characteristic odour
Physical state	Liquid
Formulation type	Emulsifiable concentrate (EC)
Guarantee	25 g/L
Container material and description	Plastic bottles, jugs, drums or tanks (0.5 L – Bulk)
Density at 20°C	1.03 g/cm^3
pH of 1% dispersion in water	4.9
Oxidizing or reducing action	No oxidizing or reducing action; no significant temperature changes were observed when the product was exposed to potassium permanganate solution (oxidizing agent), zinc powder (reducing agent), monoammonium phosphate solution (fire-extinguishing agent), turpentine or water.
Storage stability	The product is stable for 1 year when stored in plastic bottles at ambient temperature; the product is stable for 14 days at 54°C.
Corrosion characteristics	The product is non-corrosive to the packaging material.
Explodability	The product is not considered explosive.

1.3 Directions for Use

NUP6D 04 Herbicide is intended for application prior to seeding or after seeding, but before crop emergence, at a rate of 180 mL/ha (in other words, 4.5 g a.i./ha) with a non-ionic surfactant (NIS), such as Nufarm Enhance, Ag-Surf, or Merge, at a rate of 0.25% v/v in wheat (spring, durum, and winter), field corn, and soybean to control or suppress small populations of emerged weeds at up to the three-leaf stage, specifically lamb's-quarters, redroot pigweed, volunteer canola, dandelion, flixweed, wild buckwheat, kochia, and stinkweed. NUP6D 04 Herbicide may be applied once per growing season by ground application equipment.

For control of a broader spectrum of weeds, NUP6D 04 Herbicide may be applied in tank mix with a glyphosate herbicide (present as an isopropylamine or potassium salt) at a rate of 450 or 900 g a.e./ha.

1.4 Mode of Action

Pyraflufen-ethyl belongs to the phenylpyrazole chemical family and is an inhibitor of protoporphyrinogen IX oxidase (protox inhibitor), which results in the peroxidation of foliar cell membrane lipids under the presence of light, with subsequent cell membrane destruction and necrosis. Herbicidal effects of pyraflufen-ethyl are manifested as the yellowing and browning of the foliage, followed by death of the whole plant with extensive leaf burn evident. Pyraflufen-ethyl is a contact herbicide with no significant uptake by roots or emerging shoots of plants.

Pyraflufen-ethyl is classified as a Group 14 herbicide by the Weed Science Society of America and as a Group E herbicide by the Herbicide Resistance Action Committee.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in Pyraflufen-ethyl Technical have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis

Liquid chromatography methods with tandem mass spectrometry (HPLC-MS/MS) and gas chromatography methods with electron capture detector (GC-ECD), nitrogen-phosphorous detector (GC-NPD), mass spectrometry (GC-MS) and tandem mass spectrometry (GC-MS/MS) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in plant and animal matrices and environmental media. Methods for residue analysis are summarized in Appendix I, Table 1.

Gas chromatography methods with detection by mass spectrometry or tandem mass spectrometry (GC-MS or GC-MS/MS; Method 831W in plant matrices and Method AR158-97/97-183 in animal matrices) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limit of quantitation (LOQ). Acceptable recoveries (70-120%) were obtained in plant and animal matrices. The proposed enforcement methods were successfully validated in plant and animal matrices by an independent laboratory. Adequate extraction efficiencies were demonstrated using radiolabelled samples of milk and liver analyzed with the enforcement method for the animal matrices. Extraction solvents used in the plant method were similar to those used in the metabolism studies; thus, further demonstration of extraction efficiency with radiolabelled crops was not required for the enforcement method for the plant matrices.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for pyraflufen-ethyl was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices (GLP). The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to pyraflufen-ethyl.

The technical grade active ingredient pyraflufen-ethyl was of low acute toxicity by the oral route of exposure in mice and rats as well as by the dermal and inhalation routes of exposure in rats. Pyraflufen-ethyl was minimally irritating to the eyes and non-irritating to the skin of rabbits. Pyraflufen-ethyl was not a dermal sensitizer in guinea pigs.

NUP6D 04 Herbicide was of low acute toxicity by the oral, dermal and inhalation routes of exposure in rats. It was severely irritating to the eyes and extremely irritating to the skin of rabbits. NUP6D 04 Herbicide was not a potential skin sensitizer in guinea pigs.

After single or repeated administration of low doses of radiolabelled pyraflufen-ethyl, rats showed rapid but partial absorption (~56% bioavailability). Biliary excretion (36% of the administered dose [AD]) contributed to fecal excretion of radioactivity that was ~70% at the low dose, the balance being eliminated via urinary excretion (~30%). At the single or multiple oral low dose exposure, urinary excretion accounted for 27-33% of the AD suggesting that a multiple exposure regimen did not significantly affect the metabolic process. Urinary excretion was reduced to only 5-7% following a single high dose (100-fold the low dose) exposure. Excretion via the feces accounted for the remainder of the administered radioactivity in all treatment groups. Dose limited absorption occurred at the high dose, as proportionally decreased C_{max} (~38-fold *vs* low dose) and Area Under Curve (AUC; ~80-fold *vs* low or repeated dose), and increased fecal excretion (~90%) were observed. These numbers could be explained by possibly longer absorption and tissue distribution times and an increased biliary excretion at the high dose. The half-life of elimination for all dose regimens ranged from 3 to 7 hours. Excretory patterns did not exhibit gender-related variability. However, plasma and blood clearance were more rapid in females than in males as shown by the greater AUC values for males. Neither the parent compound pyraflufen-ethyl nor its metabolites appear to undergo significant tissue sequestration. Tissue burden data following oral administration of pyraflufen-ethyl did not suggest a specific target beyond the gastro-intestinal tract, liver and kidney.

The metabolic pathway in rats involved ester hydrolysis and N-demethylation. The major metabolites identified were E-1 ([2-chloro-5-(4-chloro-5-difluoromethoxy-1-methylpyrazol-3-yl)-4-fluorophenoxyacetic acid]) and E-9 ([2-Chloro-5-(4-chloro-5-difluoromethoxy-l *H* -pyrazol-3-yl)-4-fluorophenoxyacetic acid]). The metabolite E-1 was slightly acutely toxic in an oral acute toxicity study in male rats. There were no toxicology data available for the metabolite E-9, but since E-9 is an N-demethylated form of E-1, E-9 is considered to be of equal or lesser toxicity.

After repeated oral dosing, the liver [organ weight, accentuated lobular pattern, pigment deposition in Kupffer cells, periacinar hypertrophy, centrilobular swelling and vacuolation, single cell necrosis, hepatocyte proliferation], kidney [organ weight, transitional cell hyperplasia, necrosis and papillitis dilation or hyperplasia of collecting duct, acute pyelitis] and haematopoietic system [anemia, decreased haematocrit, haemoglobin concentration and red blood cell count, mean corpuscular volume and mean corpuscular hemoglobin] of rats and/or mice were the primary targets of pyraflufen-ethyl. Mice were slightly more sensitive than rats and male animals more sensitive than female animals. No treatment-related effects were observed after compound administration in the dog dosed orally up the limit dose in 28-day, 90-day or 12-month studies.

After 28-days of dermal dosing with pyraflufen-ethyl in rats, no systemic or dermal treatment-related effects were observed at any of the doses tested, up to the limit dose.

Pyraflufen-ethyl did not demonstrate genotoxic potential when tested in a battery of in vitro and in vivo genotoxicity assays including a reverse mutation assay, a gene mutation assay, a chromosomal aberration assay, a micronucleus assay and an unscheduled DNA synthesis assay.

In a dietary mouse oncogenicity study and dietary chronic/oncogenicity study in rats, liver, kidney and haematopoietic effects similar to those observed in the short-term studies, were noted, with increased severity over time. In addition to these findings, in the rat chronic/oncogenicity study, bile duct hyperplasia was observed in both sexes. Dosing was considered to be adequate in both studies and mortality was not significantly affected by the treatment.

There was no evidence of oncogenicity in the rat following treatment with pyraflufen-ethyl. Treated male mice had a significantly increased incidence of hepatocellular adenomas, as well as combined incidence of adenomas, carcinomas and/or hepatoblastomas at the mid- and high-dose when compared to control animals. The decision to combine the incidence of these tumours for the risk assessment is in agreement with the United States National Toxicology Program (NTP) studies reporting that hepatoblastomas frequently appear to arise within hepatocellular adenomas and hepatocellular carcinomas. Although there was not strong evidence of progression from these tumours to hepatoblastomas, combining these tumours should be considered in an overall evaluation for hazard identification studies (Turusov et al. 2002). In treated female mice, an increased incidence of hepatocellular adenomas as well as combined incidence of adenomas, carcinomas and/or hepatoblastomas was observed at the high dose only, when compared to control animals. Several non-guideline mechanistic studies were submitted within the context of a Mode of Action (MOA) document; however the MOA was not fully articulated and focused mainly on the description of hepatocyte necrosis/proliferation cycles to explain the oncogenicity findings, and it did not address the key events. The absence of this important information makes it difficult to draw conclusions regarding the MOA for tumour formation in mice, and, consequently, the relevance to humans. In view of the uncertainty regarding the MOA, it was considered appropriate to use a linear approach (low dose extrapolation) for the cancer risk assessment.

In a 2-generation reproductive toxicity study in rats, offspring toxicity was observed at the same dose at which maternal toxicity was observed. Body weight effects, liver and kidney toxicity were observed in the dams, whereas only body weight effects were observed in the young. There was no evidence of sensitivity of the young. There was no evidence of reproductive toxicity.

In the rat oral developmental toxicity study, no treatment-related effects were observed in the dams or in fetuses up to and including the limit dose.

In the rabbit oral developmental toxicity study, maternal toxicity was observed at the mid-dose with gastro-intestinal tract lesions, and mortality (GD 17-19), which was preceded by agonal signs of death. Mortality was also observed at the high-dose (GD 16-24). Complete litter resorptions and abortions occurred at the high dose. There was no evidence of malformations or sensitivity of the young.

The acute oral neurotoxicity study as well as the 90-day oral neurotoxicity study in rats did not demonstrate any neurotoxicity. In both studies, transient body weight effects were observed.

In an immunotoxicity study, pyraflufen-ethyl affected the immune response in male rats at a very high dose.

Results of the toxicology studies conducted on laboratory animals with pyraflufen-ethyl and its associated end-use product are summarized in Appendix I, Tables 2 and 3. The toxicology endpoints for use in the human health risk assessment are summarized in Appendix I, Table 4.

Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found in the Pesticides and Pest Management portion of Health Canada's website at www.healthcanada.gc.ca/pmra. Incidents were searched and reviewed for pyraflufen-ethyl. Any additional information submitted by the applicant during the review process was considered. As of 4 November 2013, no health-related incidents involving pyraflufen-ethyl were reported to the PMRA.

3.1.1 *Pest Control Product Act* Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the standard complement of required studies was available for pyraflufen-ethyl including developmental toxicity studies in rats and rabbits and a reproductive toxicity study in rats.

With respect to potential prenatal and postnatal toxicity, in a rat 2-generation dietary reproductive toxicity study and in a rat developmental oral toxicity study, fetuses did not show evidence of sensitivity (compared to parents) or malformations when exposed to pyraflufen-ethyl. In the rabbit developmental oral toxicity study, effects of a serious nature were observed. Abortions and complete litter resorption were observed at the highest dose tested in the presence of maternal toxicity. No effects were observed in the fetus at lower doses, while the dams were affected by gastro-intestinal tract lesions and death. Endpoints in the young were well-characterized and adverse effects occurred at maternally toxic doses. In rabbits, the maternal no observed adverse effect level (NOAEL) provided an inherent 3-fold margin to the developmental NOAEL and the serious effects noted. On the basis of the overall information, the *Pest Control Product Act* factor was reduced to 1-fold.

3.2 Determination of Acute Reference Dose

No acute endpoints of concern were identified in the toxicology database; therefore, an acute reference dose was not established.

3.3 Determination of Acceptable Daily Intake (ADI)

To estimate risk of repeat dietary exposure, two co-critical studies were identified for the risk assessment. The 18-month dietary oncogenicity study in mice with a NOAEL of 20 mg/kg bw/day was selected for risk assessment. The rabbit oral developmental toxicity study also with a NOAEL of 20 mg/kg bw/day was determined to be co-critical in the establishment of the ADI. In the oncogenicity study, at the lowest observed adverse effect level (LOAEL) of 98 mg/kg bw/day, increased incidence of liver pathology was observed. In the rabbit oral developmental toxicity study, at the maternal LOAEL of 60 mg/kg bw/day, body weight effects, GI tract lesions and death were observed. The co-critical studies provide the lowest NOAELs in the database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the *Pest Control Product Act* Hazard Characterization section, the *Pest Control Product Act* factor was reduced to 1-fold.

The composite assessment factor (CAF) is therefore 100.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{20 \text{ mg/kg bw/day}}{100} = 0.2 \text{ mg/kg bw/day of pyraflufen-ethyl}$$

The ADI provides a margin of 750 to the dose at which resorption and abortions occurred in the rabbit oral developmental toxicity study.

Cancer Assessment

An increase incidence of benign tumours was observed in male mice at 110 mg/kg bw/day and in both sexes at 547/524 mg/kg bw/day (males/females). Pyraflufen-ethyl was not genotoxic. In view of the uncertainty regarding the mode of action leading to the observed tumours in mice, it was considered appropriate to use a linear approach (low dose extrapolation) to the cancer risk assessment. The Unit risk for pyraflufen-ethyl, denoted by q_1^*, was calculated for the combined hepatocellular adenomas, carcinomas and hepatoblastomas in male mice ($q_1^* = 1.57 \times 10^{-2}$ (mg/kg bw/day)$^{-1}$).

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Short- and Intermediate-term Dermal

For short-, and intermediate-term dermal risk assessment, the 28-day dermal study in rats was selected as an appropriate study. The study comprised an assessment of the most sensitive parameters including liver pathologies and mortality. In the rabbit oral developmental study, developmental effects (abortions, resorptions) occurred at a dose higher than that causing death in the maternal animals. Therefore, use of the dermal study is considered protective of the developmental effects. In absence of adverse effects at the highest dose tested, a NOAEL was established at 1000 mg/kg bw/day. The target margin of exposure for this endpoint is 100. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and unborn children.

Occupational exposure to NUP6D 04 Herbicide is characterized as short to intermediate-term and is predominantly by the dermal and inhalation routes.

Short- and Intermediate-term Inhalation

For short- and intermediate-term inhalation assessment, the developmental oral toxicity study in rabbits was selected. At the maternal LOAEL of 60 mg/kg bw/day, decreased body weight, gastro-intestinal tract lesions and deaths were observed in dams. A NOAEL of 20 mg/kg bw/day was established. The target margin of exposure for this endpoint is 100. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and unborn children.

3.4.1.1 Dermal Absorption

A default dermal absorption factor of 100% was assumed for the cancer risk assessment. As the non-cancer dermal risk was based on a dermal endpoint, a dermal absorption factor was not required.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Mixer/loader/applicator Exposure and Risk Assessment

Individuals have potential for exposure to NUP6D 04 Herbicide during mixing, loading and application. Dermal and inhalation exposure estimates for workers mixing, loading and applying using groundboom application equipment were generated using unit exposure values from PHED version 1.1 and default area treated per day values, as chemical-specific data for assessing human exposures during pesticide handling activities were not submitted. The exposure estimates are based on mixers/loaders/applicators wearing a single layer of clothing and chemical resistant gloves when mixing and loading.

Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight.

For non-cancer risk estimates, exposure estimates were compared to the toxicological endpoints (NOAEL) to obtain the MOE; the target MOE is 100.

The lifetime average daily dose (LADD) was used to calculate cancer risk for chemical handlers mixing/loading and applying NUP6D 04 Herbicide. As a tier one worst case estimate it was assumed that chemical handlers would be exposed for 30 days per year. For farmers in particular this is likely an over estimate since only one application per year is expected early in the season pre-emergence.

Calculated MOEs were above the target MOE of 100 (Table 3.4.2.1) and cancer risk was below 1×10^{-5} (Table 3.4.2.2) which is not considered to be of concern for occupational exposure.

Table 3.4.2.1.1 Mixer/loader/applicator non-cancer risk assessment for chemical handlers

Exposure scenario	PHED unit exposure (µg/kg a.i. handled)		ATPD (ha/day)†	Daily exposure (mg/kg bw/day)‡		MOE¶	
	Dermal	Inhalation		Dermal	Inhal	Dermal	Inhal
PPE: Single layer (and gloves when mixing/loading)							
Groundboom farmer	84.12	2.56	107	0.000506	0.000015	1975124	1298027
Groundboom custom	84.12	2.56	360	0.0017	0.000052	587051	385802

† Default Area Treated Per Day

‡ Daily exposure = (PHED unit exposure × ATPD × Rate (0.0045 kg a.i./ha)) / (80 kg bw × 1000 µg/mg)

¶ Based on a Dermal NOAEL = 1000 and an Inhalation NOAEL = 20 mg/kg bw/day, target MOE = 100

Table 3.4.2.1.2 Mixer/loader/applicator cancer risk assessment for chemical handlers

Exposure scenario	PHED unit exposure (µg/kg a.i. handled)		ATPD (ha/day)†	Daily exposure (mg/kg bw/day)‡	LADD¶	Cancer Risk**
	Dermal	Inhalation				
PPE: Single layer (and gloves when mixing/loading)						
Groundboom farmer	84.12	2.56	60	0.00029	1.2×10^{-5}	1.9×10^{-7}
Groundboom custom	84.12	2.56	240	0.0012	4.9×10^{-5}	7.7×10^{-7}

† Default Area Treated per Day

‡ Daily exposure = (PHED unit exposure × ATPD × Rate (0.0045 kg a.i./ha)) / (80 kg bw × 1000 µg/mg)

¶ LADD = (Daily exposure × Exposure Duration (30 days) × years of exposure (40 years)) / (365 days/year × Life Expectancy (78 years))

** Cancer risk = LADD × q_1* Where q_1* = 1.57×10^{-2} (mg/kg bw/day) $^{-1}$

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

NUP6D 04 Herbicide is designed for use as a contact herbicide for broadleaf weed control and will damage emerged crop plants. As such, it is proposed to be applied prior to the emergence of the crop, either as a pre-seeding or post-seeding application and no foliar contact is expected. Therefore, postapplication exposure is expected to be minimal and a quantitative risk assessment was not conducted.

3.4.3 Residential Exposure and Risk Assessment

Bystander exposure should be negligible since the potential for drift is expected to be minimal. Application is limited to agricultural crops only when there is low risk of drift to areas of human habitation or activity such as houses, cottages, schools and recreational areas, taking into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition for risk assessment and enforcement in plant products and animal commodities is pyraflufen-ethyl and metabolite E-1. The data gathering/enforcement analytical method is valid for the quantitation of pyraflufen-ethyl and E-1 residues in crop and livestock matrices. The total residues of pyraflufen-ethyl and metabolite E-1 are stable in cotton hulls, meal and refined oil for up to 2 months, in corn forage, stover and grain for up to 4 months, in soybean forage, hay and seed for up to 6 months, in cotton seed and gin byproducts for up to 6-7 months, in wheat grain for up to 13 months, in wheat straw for up to 17 months and in wheat forage and hay for up to 3.6 years when stored in a freezer at -20°C. The raw agricultural commodities of field corn, soybeans and wheat were processed, but were not further analyzed due to the lack of quantifiable residues. Adequate feeding studies were carried out to assess the anticipated residues in livestock matrices resulting from the current uses; quantifiable residues are not expected to occur in livestock matrices with the current use pattern. Crop field trials conducted throughout the United States, including representative Canadian growing regions, using end-use products containing pyraflufen-ethyl at approved or exaggerated rates in or on field corn, soybeans and wheat are sufficient to support the proposed maximum residue limits.

3.5.2 Dietary Risk Assessment

Chronic (cancer and non-cancer) dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.14), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

3.5.2.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the basic chronic non-cancer analysis for pyraflufen-ethyl: 100% crop treated, default processing factors, residues of crop and animal commodities based on MRL and/or American tolerance levels. The basic chronic dietary exposure from all supported pyraflufen-ethyl food uses (alone) for the total population, including infants and children, and all representative population subgroups is less than 1% of the ADI. Aggregate exposure from food and drinking water is considered acceptable. The PMRA estimates that chronic dietary exposure to pyraflufen-ethyl from food and drinking water is less than 1% (0.000268 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for children 1-2 years old at less than 1% (0.001137 mg/kg bw/day) of the ADI.

The intermediate refined chronic cancer risk assessment was conducted with the same criteria used for the chronic non-cancer assessment; however, MRLs for animal commodities were not included since residues are not expected in livestock matrices with the Canadian use pattern. The lifetime cancer risk from exposure to pyraflufen-ethyl in food and drinking water was estimated to be 1.5×10^{-6} for the general population, which is not of health concern.

3.5.2.2 Acute Dietary Exposure Results and Characterization

No appropriate endpoint attributable to a single dose for the general population (including children and infants) was identified.

3.5.3 Aggregate Exposure and Risk

The aggregate risk for pyraflufen-ethyl consists of exposure from food and drinking water sources only; there are no residential uses.

3.5.4 Maximum Residue Limits

Table 3.5.1 Proposed Maximum Residue Limits (MRLs)

Commodity	Recommended MRL (ppm)
Dry soybeans	0.01
Field corn	0.01
Wheat	0.01
Eggs; Milk; Fat, meat and meat byproducts of cattle, goat, hogs, horses, poultry and sheep	0.02

For additional information on Maximum Residue Limits (MRLs) in terms of the international situation and trade implications, refer to Appendix II.

The nature of the residues in animal and plant matrices, analytical methodologies, field trial data, and acute and chronic dietary risk estimates are summarized in Appendix I, Tables 1, 5 and 6.

3.6 Exposure from Drinking Water

3.6.1 Concentrations in Drinking Water

Estimated Concentrations in Drinking Water Sources: Level 1 Modelling

Estimated environmental concentrations (EECs) of the combined residue in potential drinking water sources (groundwater and surface water) were generated using computer simulation models. Four transformation products (E-1, E-2, E-3 and E-9) were included in this level 1 drinking water modelling. An overview of how the EECs are estimated is provided in the PMRA's Science Policy Notice SPN2004-01, *Estimating the Water Component of a Dietary Exposure Assessment*. EECs of the combined residue in groundwater were calculated using the PRZM-GW model to simulate leaching through a layered soil profile over a 50-year period. The concentrations calculated using PRZM-GW are based on the flux, or movement, of pesticide into shallow groundwater with time. EECs of the combined residue in surface water were calculated using the PRZM/EXAMS model, which simulate pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body. Pesticide concentrations in surface water were estimated in two types of vulnerable drinking water sources, a small reservoir and a prairie dugout.

A Level 1 drinking water assessment was conducted using conservative assumptions with respect to environmental fate, application rate and timing, and geographic scenario. The Level 1 EEC estimate is expected to allow for future use expansion into other crops at this application rate. Appendix I, Table 7 lists the application information and main environmental fate characteristics used in the simulations. A number of initial application dates between March 1 and June 15 were modelled. The model was run for 50 years for all scenarios. The largest EECs of all selected runs are reported in Table 1 below.

Table 3.6.1 Level 1 estimated environmental concentrations of pyraflufen-ethyl combined residue in potential drinking water sources

Compound	Groundwater EEC (μg a.i./L)		Surface Water EEC (μg a.i./L)			
			Reservoir		Dugout	
	Daily[1]	Yearly[2]	Daily[3]	Yearly[4]	Daily[3]	Yearly[4]
The combined residue	0.62	0.61	0.25	0.060	0.66	0.56

[1] 90th percentile of daily average concentrations
[2] 90th percentile of yearly average concentrations
[3] 90th percentile of yearly peak concentrations
[4] 90th percentile of yearly average concentrations

Water Monitoring Data

In addition to water modelling, a search for water monitoring data on pyraflufen-ethyl in Canada was undertaken. This chemical is not currently registered for use in Canada, as such; no monitoring data for pyraflufen-ethyl in Canada are expected.

United States databases were also searched for data on pyraflufen-ethyl in water as it is registered in the United States. Data on residues present in water samples taken in the United States are important to consider in the Canadian water assessment given the extensive monitoring programs that exist in the United States. Runoff events, local use patterns, site specific hydrogeology as well as testing and reporting methods are probably more important influences on residue data rather than Northern versus Southern climate. As for the climate, if temperatures are cooler, residues may break down more slowly, on the other hand if temperatures are warmer, growing seasons may be longer and applications may be more numerous and frequent.

Pyraflufen-ethyl is not on the analyte list of the various US databases that were searched including the United States Geological Survey National Water Quality Assessment program (NAWQA), the United States Environmental Protection Agency's Storage and Retrieval (STORET) data warehouse, the United States Department of Agriculture Pesticide Data Program for either surface water or groundwater or the National Stream Quality Accounting Network (NASQAN). These results are expected given that pyraflufen-ethyl transforms rapidly in the environment.

Discussions and Conclusions

Level 1 drinking water exposure estimates determined using modelling are presented in Section 3.6.

Given the rapid dissipation of pyraflufen-ethyl in the environment it is unlikely that the active ingredient would be detected in water. Information on the detection of transformation products in water is not available. The concentrations estimated via modelling should be considered in the human health dietary risk assessment.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Data on the fate and behaviour of pyraflufen-ethyl and its major transformation products are summarized in Appendix I, Tables 8 and 9.

Pyraflufen-ethyl enters the environment when used as an herbicide for control of weeds on a variety of crops. When applied, pyraflufen-ethyl will primarily come in contact with soil. It is carried from the area of application by drift and run-off. In both soil and water, pyraflufen-ethyl transforms quickly, with biotransformation being the major route of dissipation and with hydrolysis and phototransformation contributing to a lesser extent. Major transformation products include E-1, E-2 and E-3. The transformation product E-1 is soluble, mobile and moderately persistent and is expected to reach ground and surface water. The transformation products E-2 and E-3 are persistent in soil and aquatic systems and tend to adsorb to soil and sediment, with residues in soil carrying over to the next season and accumulating over time.

Pyraflufen-ethyl has low mobility in soil and is not expected to leach. The transformation product E-1 is moderately to highly mobile in soil and meets the criteria for a leacher and borderline leacher. The transformation products E-2 and E-3 are classified as having slight to low mobility and are not expected to leach. In laboratory studies, pyraflufen-ethyl and E-1 did not leach below 15 cm and essentially none of the applied material was found in the leachate collected from the soils. Due to the low leaching potential of pyraflufen-ethyl and transformation products E-2 and E-3, they are expected to have a low potential to reach groundwater or to reach surface waters throuh runoff. However, because some of the transformation products are persistent in soil, groundwater modelling indicates that residues can reach groundwater after a period of continued use.

In field studies, pyraflufen-ethyl dissipated quickly, having a half-life of less than one day. The major transformation products observed were El and E-3. The study from Washington showed both major transformation products were persistent. Leaching was limited, with nearly all residues being detected in the top 15 cm soil layer. This is in agreement with laboratory studies where a similar accumulation of the above transformation products was observed, and a similar lack of extensive leaching. These results show that major transformation products are persistent in soil, and carryover of pyraflufen-ethyl residues from season to season can be expected, resulting in accumulation in the soil.

In water, pyraflufen-ethyl is rapidly transformed (half-life of < 6 hours) by microorganisms in aerobic and anaerobic aquatic systems. The major transformation products include E-1, which is moderately persistent in the water phase and E-2, which partitions to sediment in addition to the minor transformation product E-3. All three transformation products are persistent and could accumulate over time.

Available information on the transformation product E-1 indicates that it has low bioconcentration potential in rainbow trout. No information on the bioconcentration potential of the transformation product E-3 was submitted and this information is required.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. EECs are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications (Appendix I, Tables 10, 11 and 12). Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (in other words, protection at the community, population, or individual level) (Appendix I, Tables 13, 14 and 15).

Taxonomic group	Exposure	Endpoint	Species Uncertainty Factor
Earthworm	Acute	LC_{50}	0.5
	Chronic	NOEC	1
Other non-target arthropods	Acute	LR_{50}	LOC of 2 (screening level)
Birds	Acute oral	LD_{50}	0.1
	Dietary	LD_{50}	0.1
	Reproduction	NOEL	1
Mammals	Acute oral	LD_{50}	0.1
	Reproduction	NOEL	1
Non-target terrestrial plants	Acute	EC_{25}, or HR_5 of SSD of ER_{50}*	1
Aquatic invertebrates	Acute	LC_{50} or EC_{50}	0.5
	Chronic	NOEC	1
Fish	Acute	LC_{50}	0.1
	Chronic	NOEC	1
Amphibians	Acute	Fish LC_{50}	0.1
	Chronic	Fish NOEC	1
Algae	Acute	EC_{50}	0.5
Aquatic vascular plants	Acute	EC_{50}	0.5

* 5th percentile hazard rate of the species sensitivity distribution of ER_{50} values

** The LOC for bees is set to 0.4.

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC = 1, except for *T. pyri* and *Aphidius* screening level studies which have an LOC=2, and bees which have an LOC=0.4). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risks to Terrestrial Organisms

Risk of pyraflufen-ethyl (including the end-use product) to terrestrial organisms was based upon evaluation of toxicity data for the following (Appendix I, Table 16):

- Acute and chronic studies with mammal and bird species representing vertebrates.
- Acute and chronic studies using the technical grade active ingredient for earthworms.
- Acute oral and contact studies using the technical grade active ingredient and end-use product with bees.
- Acute contact studies with beneficial arthropods.
- Seedling emergence and vegetative vigour studies using the end-use product on terrestrial vascular plants.

Terrestrial invertebrates

Soil dwelling arthropods (Earthworms)

Pyraflufen-ethyl is not toxic to earthworms and is not expected to pose a risk.

Bees

Contact exposure: Risk to bees was calculated using results from an acute toxicity test with the TGAI and a separate test with the formulated end-use product ET-751 2.5% EC. Although the end-use product had adverse effects on bee survival, the level of concern was not exceeded and the RQ was <0.1 (Appendix I, Table 16).

Oral exposure: For the oral exposure route, the TGAI toxicity endpoint was used to determine risk as the end-use product formulation is not expected to be found in food items. Based on available information, the use of pyraflufen-ethyl is not expected to pose an acute oral or contact risk to bees (Appendix I, Table 16).

Larval bee toxicity: As exposure of bee larvae to the formulated end-use product is not expected due to rapid dissipation from the site of application, toxicity is not a concern. It is unlikely that bees would pick up end-use product material from food and pollen and carry it back to the hive where long term exposure could result.

Predators and parasites: Beneficial insects

Toxicity data available for predatory mites and parasitic wasps indicates both acute and reproductive sensitivity to the end-use product. Based on the empirical toxicity value of LD_{50} <1.6L end-use product/ha and the application rate of 0.18 end-use product/ha, risk could not be determined for beneficial insects ($RQ > 0.11$). The PMRA cannot determine if the LOC is exceeded as the only available study had a single exposure dose which showed significant adverse effects. Therefore, it is assumed that beneficial insects will be adversely affected by the formulated end-use product and a mitigative label statement will be required.

Terrestrial vertebrates

Birds

Birds showed no adverse effects to pyraflufen-ethyl from either acute oral exposure or dietary intake through food. When mallard ducks were exposed chronically through food, significant reproductive effects were noted with a NOAEL of 324 ppm diet. This toxicity endpoint is equivalent to a daily exposure of 18.3 mg a.i./kg bw/d, which, when compared to an EDE of ≤ 0.226 a.i./kg bw/d, results in an RQ of < 0.1. Based on the proposed application rate, there is negligible acute and chronic risk to birds from exposure to pyraflufen-ethyl (Appendix I, Table 17).

Mammals

Pyraflufen-ethyl and the formulated end-use product are practically non-toxic to mammals acutely and no risk is expected. Adverse chronic effects were seen in rats in a two generation reproduction study with the TGAI (toxic to adults and offspring at 1000 ppm in the diet); however; no reduction was observed in the production of young at up to 10,000 ppm in the diet. There are negligible acute or chronic risks to small mammals from the use of pyraflufen-ethyl (Appendix I, Table 17).

Terrestrial plants

Non-target Vascular Plants

Crop plants are sensitive to the formulated end-use product and a potential risk was determined based on an overspray scenario for non-target plants (RQ = 23.7 for plant vigor). Mitigative measures, in the form of buffer zones, will be required to protect non-target terrestrial plants.

A Tier II spray drift assessment was conducted for terrestrial plants and indicated that non-target plants within 1m of a treated field would be exposed to pyraflufen-ethyl concentrations exceeding the LOC (RQ = 1.4) (Appendix I, Table 16).

4.2.2 Risks to Aquatic Organisms

Risk of pyraflufen-ethyl (including the end-use product and the transformation product E-1) to aquatic organisms was based upon evaluation of toxicity data for the following (Appendix I, Table 18):

- Acute and chronic invertebrate study with technical grade active ingredient and transformation product E-1
- Acute invertebrate study with the formulated end-use product
- Acute studies using two freshwater fish species (bluegill sunfish, rainbow trout) with the technical grade active ingredient, end-use product and transformation product E-1
- Chronic studies using fathead minnow with the technical grade active ingredient and the transformation product E-1. This information was used as a surrogate for the amphibian risk assessment
- 2 algal species, diatom and a vascular plant (duckweed) with information provided on the end-use product, technical grade active ingredient and transformation product E-1

Risk of pyraflufen-ethyl (including the end-use product) to marine organisms was based upon evaluation of toxicity data for the following (Appendix I, Tables 18):

- Acute invertebrate studies with the Eastern oyster and mysid shrimp using the technical grade active ingredient and transformation product E-1.
- An acute fish toxicity of the sheepshead minnow using the technical grade active ingredient and the transformation product E-1
- An acute study of marine diatom using the formulated end-use product

Aquatic organisms could be exposed to pyraflufen-ethyl from drift or runoff. At the screening level, expected environmental concentrations are calculated based on a direct application to water at the maximum cumulative rate, thus taking into account the maximum labelled application rate, the application interval and the dissipation of the compound in aquatic systems. Bodies of water of two depths are considered for the risk assessment. A depth of 15 cm is representative of a seasonal water body used by amphibians during the reproduction period. A depth of 80 cm is representative of a permanent water body for all other aquatic organisms. The screening level EECs are based on the maximum seasonal application rate of 4.5 g a.i./ha (see Table 10). The EECs were determined to be 0.56 µg a.i./L in 80 cm water and 3.0 µg a.i./L in 15cm water.

Refined aquatic risk assessments were conducted for a spray drift scenario (6% off field deposition rate based on ground boom application with medium droplet size) and a runoff scenario. The EECs for drift were 0.034 µg/L (80 cm water depth) and 0.18 µg a.i./L (15 cm water depth). The EECs used for runoff risk determination were the peak concentration (0.43 µg a.i./L for 80 cm water depth) and the 21 day mean concentration (1.2 µg a.i./L for 15 cm water depth).

Water modelling for runoff was determined using a conservative exposure scenario for the combined residues relevant to the environment (as described in section 3.6). With this assessment approach, runoff from the site of application would be expected to result in the exceedance of the LOC for amphibians and freshwater algae from exposure to the parent chemical. However, when exposure to the transformation product E-1 is considered, the level of concern is not exceeded. Therefore, although there is uncertainty around the toxicity of the transformation products E-2 and E-3, the E-1 transformation product is most likely to be found in water, and it may be assumed that risk to aquatic organisms from runoff of pyraflufen-ethyl is relatively low. In order to reduce runoff into surface waters, label statements are required on the product labels to inform users of the potential risks.

Freshwater invertebrates

At the screening level, the risks of pyraflufen-ethyl and the end-use product to freshwater invertebrates did not exceed the level of concern (RQ<0.1).

Fish and amphibians

At the screening level, the level of concern was not exceeded for freshwater fish from the use of the technical grade active ingredient, the formulated end-use product or the transformation product E-1. A risk was identified at the screening level for amphibians, based on the early life stage study of fathead minnow (RQ=3.4). Refined risk assessments using EEC values for drift and runoff water modelling resulted in RQ values of 0.2 and 1.3, respectively. As the level of concern was exceeded for the refined runoff assessment, amphibians may be at risk from concentrations of pyraflufen-ethyl in runoff water. Mitigation in the form of spray buffer zones will be required and runoff reduction statements will be put on the label.

Freshwater algae and plants

The level of concern was exceeded at the screening level for algae, with an RQ of 3.5. Refined risk assessments using EEC values for drift and runoff water modelling resulted in RQ values of 0.2 and 2.7, respectively. As the level of concern was exceeded for the refined runoff assessment, algae may be at risk from residues of pyraflufen-ethyl in runoff water. Mitigation in the form of spray buffer zones will be required.

Marine organisms

The level of concern was not exceeded for marine invertebrates and fish in a screening level risk assessment using the technical grade active ingredient. The level of concern was not exceeded for marine algae in a screening level risk assessment using the transformation product E-1.

4.2.3 Incident Reports

No incident reports were found in a search conducted using available databases (PMRA incident reporting, USEPA Environmental Incident Information System database v. 2).

5.0 Value

5.1 Effectiveness Against Pests

Efficacy information submitted for review included data from 22 field trials conducted in Alberta, Manitoba, and Saskatchewan during a three year period. All trials were adequately designed and conducted on a variety of soils. The efficacy of NUP6D 04 Herbicide applied alone at 3 to 9 g a.i./ha with or without a NIS or in tank mix with a glyphosate herbicide (present as the isopropylamine or potassium salt) was assessed at up to four times throughout the growing season for control of volunteer canola, dandelion, flixweed, wild buckwheat, kochia, stinkweed, lamb's-quarters, redroot pigweed, and annual sow-thistle. The herbicide treatments were applied using small plot application equipment. Nineteen of the 22 trials were conducted in summerfallow and the remaining three trials were conducted in cropland, in other words, fields treated with NUP6D 04 Herbicide were subsequently seeded to spring wheat and lentil.

5.1.1 NUP6D 04 Herbicide as an Alone Treatment

Adequate information was submitted to support the efficacy claims summarized in Table 5.1.1 for NUP6D 04 Herbicide applied with a NIS.

Table 5.1.1 Acceptable efficacy claims for NUP6D 04 Herbicide applied with a NIS

Treatment	Acceptable claims
NUP6D 04 Herbicide at 4.5 g a.i./ha applied with a NIS at 0.25% v/v, such as Nufarm Enhance, Agral 90, or Ag-Surf.	For small populations of weeds at up to the 3-leaf stage: Control of lamb's-quarters and redroot pigweed. Suppression of volunteer canola, dandelion, flixweed, wild buckwheat, kochia, and stinkweed.

5.1.2 NUP6D 04 Herbicide Applied in Tank Mix with a Glyphosate Herbicide

Adequate information was provided to support the efficacy claims summarized in Table 5.1.2 for the tank mixture of NUP6D 04 Herbicide plus a glyphosate herbicide.

Table 5.1.2 Acceptable efficacy claims for NUP6D 04 Herbicide applied in tank mix with a glyphosate herbicide

Products	Weed claims
NUP6D 04 Herbicide at 4.5 g a.i./ha in tank mix with a glyphosate herbicide (present as the isopropylamine or potassium salt) at 450 or 900 g a.e./ha.	All weeds controlled by NUP6D 04 Herbicide alone and by a glyphosate herbicide alone.

5.2 Phytotoxicity to Host Plants

Crop safety information submitted included scientific rationales and data from two relevant GLP controlled environmental studies conducted in Massachusetts and one field trial conducted in Manitoba.

In the GLP studies, the tolerance of ten species, including four monocotyledonous crops: corn, oat, onion, and perennial ryegrass; and six dicotyledonous crops: cabbage, cucumber, lettuce, soybean, tomato, and turnip, to NUP6D 04 Herbicide applied at up to 10 g a.i./ha was assessed. Herbicide treatments were sprayed onto the surface of root medium in pots using an application chamber constructed with an overhead atomizing spray device and a revolving belt which transports the pots passing through the spray device. Following herbicide treatments, the pots were subsequently seeded to these crops previously mentioned and then placed in controlled environmental chambers. Percent seed germination and shoot length and weight were measured at two weeks after seeding.

In the field trial, injury to spring wheat and lentil was assessed following a pre-plant application of up to 12 g a.i./ha NUP6D 04 Herbicide alone and in tank mix with a glyphosate herbicide at up to 900 g a.e./ha.

5.2.1 Supported Host Claims

Crop safety information was adequate to support host tolerance claims for wheat (spring, durum, and winter), field corn, and soybean for NUP6D 04 Herbicide applied prior to crop emergence at 4.5 g a.i./ha with a NIS at 0.25% v/v. This information is summarized below.

- Pyraflufen-ethyl is a contact herbicide with no significant uptake by roots or emerging shoots of plants and with limited translocation in plants. Pyraflufen-ethyl provides control of emerged weeds only.

- Data from the GLP controlled environmental studies demonstrated that soybean and field corn exhibited an adequate margin of crop safety to a pre-seeding application of NUP6D 04 Herbicide at up to 10 g a.i./ha.

- Data from the field trial demonstrated that injury to spring wheat was not visually detectable for pre-plant applications of up to 12 g a.i./ha NUP6D 04 Herbicide alone or in tank mix with a glyphosate herbicide at up to 900 g a.e./ha.

5.3 Supported Host Claims

Pyraflufen-ethyl acts on plants by contact only with no significant uptake by roots and emerged shoots of plant and with limited translocation within plant. Therefore, unacceptable damages to crops due to the absorption of pyraflufen-ethyl via plant roots and emerging shoots from soil would not be expected.

Crop safety information from the GLP controlled environmental studies and the field trial confirmed that all of the evaluated five monocotyledonous crops and seven dicotyledonous crops exhibited adequate margins of crop safety to pre-plant application of NUP6D 04 Herbicide alone at 4.5 g a.i./ha or in tank mix with a glyphosate herbicide at up to 900 g a.i./ha. This information can be extrapolated to support the tolerance claims for the rotational crops.

5.4 Economic Benefit

Herbicide application prior to crop emergence is an effective method to manage weeds to permit optimal crop emergence and establishment. Glyphosate herbicide has been widely used to control weeds as a pre-seeding application. However, the majority of volunteer canola is glyphosate-tolerant (Roundup-Ready). Therefore, tank mixing glyphosate with other herbicides, such as pyraflufen-ethyl that have a different mode of action and that do not possess residual activity, can provide effective weed control without negatively impacting the crop.

5.5 Sustainability

5.5.1 Survey of Alternatives

A few pre-emergence herbicides are registered for use in one or more of corn, soybean, and wheat for control of emerged weeds. These herbicides include Group 14 herbicides, for example, Aim EC Herbicide (Registration Number 28573; 240 g/L carfentrazon-ethyl) and Eragon Herbicide (Registration Number 29372; 70% saflufenacil). However, none of them belong to the same chemical family as pyraflufen-ethyl (the phenylpyrazoles).

5.5.2 Compatibility with Current Management Practices Including Integrated Pest Management

A single application of NUP6D 04 Herbicide offers control or suppression of select emerged broadleaf weeds prior to the emergence of wheat (spring, durum, and winter), field corn, and soybean. It is compatible with integrated weed management practices and with both conservation tillage and conventional tillage systems.

5.5.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

Repeated use of herbicides having the same mode of action in a weed control program increases the probability of selecting naturally resistant biotypes. As pyraflufen-ethyl is a Group 14 herbicide that belongs to a new chemical family, it may contribute to the management of broadleaf weeds that are not cross-resistant to other Group 14 herbicides as well as contributing to resistance management in the same manner as other Group 14 herbicides.

Herbicide-resistant populations of several broadleaf weed species have been discovered and are variously resistant to herbicides, including those that belong to Weed Science Society of America Group 2 (acetolactate synthase inhibitors), Group 4 (synthetic auxins), Group 5 (inhibitors of photosynthesis at photosystem II), Group 7 (inhibitors of photosynthesis at photosystem II), Group 9 (EPSP synthase inhibitors), and Group 22 (photosystem I electron diversion).

When applied at the labeled use rate, NUP6D 04 Herbicide is expected to control or suppress biotypes of labeled weeds that are resistant to other groups of chemistries. Consequently, pyraflufen-ethyl has the potential to delay the onset of herbicide resistance and to combat certain forms of resistance once present, by means of tank mixing and/or rotation with herbicides of other modes of action.

The label of NUP6D 04 Herbicide includes the resistance management statements, as per Regulatory Directive DIR99-06, *Voluntary Pesticide Resistance-Management Labeling Based on Target Site/Mode of Action*.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy: in other words, persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, pyraflufen-ethyl and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[4] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Pyraflufen-ethyl does not meet Track 1 criteria, and is not considered a Track 1 substance. See Appendix I, Table 19 for comparison with Track 1 criteria.
- Pyraflufen-ethyl does not form any transformation products that meet all Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*[5]. The list is used as described in the PMRA Notice of Intent NOI2005-01[6] and is based on existing policies and regulations including DIR99-03 and DIR2006-02,[7] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

> The end-use product NUP6D 04 Herbicide does not contain any formulants of health or environmental concern identified in the *Canada Gazette*. However, the end-use product does contain an aromatic petroleum distillate. Therefore, the label for the end-use product NUP6D 04 Herbicide will include the statement: "This product contains aromatic petroleum distillates that are toxic to aquatic organisms."

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and DIR2006-02.

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[4] DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

[5] *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

[6] NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

[7] DIR2006-02, *Formulants Policy and Implementation Guidance Document.*

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for pyraflufen-ethyl is adequate to define the majority of toxic effects that may result from exposure. There was no evidence of increased susceptibility of the young in reproduction or developmental toxicity studies. Pyraflufen-ethyl affected immune response in male rats at a very high dose. There was no evidence of neurotoxicity. There was no evidence on oncogenicity in rats after long-term dosing. Pyraflufen-ethyl was not a mutagen. There was evidence of carcinogenicity in mice after longer-term dosing. In short-term and chronic studies on laboratory animals, the primary targets were the liver, kidney and haematopoietic system. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Mixers, loaders and applicators handling NUP6D 04 Herbicide and workers re-entering treated areas are not expected to be exposed to levels of NUP6D 04 Herbicide that will result in health risks of concern when NUP6D 04 Herbicide is used according to label directions. The personal protective equipment on the product label is adequate to protect workers.

The nature of the residues in plants and animals is adequately understood. The residue definition for enforcement and risk assessment is pyraflufen-ethyl and metabolite E-1 in plant products and in animal matrices. The use of pyraflufen-ethyl on field corn, soybeans and wheat does not constitute a risk of concern for chronic (cancer and non-cancer) dietary exposure (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend MRLs. The PMRA recommends that the following MRLs be specified for residues of pyraflufen-ethyl and metabolite E-1.

Commodity	Recommended MRL (ppm)
Dry soybeans	0.01
Field corn	0.01
Wheat	0.01
Eggs; Milk; Fat, meat and meat byproducts of cattle, goat, hogs, horses, poultry and sheep	0.02

7.2 Environmental Risk

Pyraflufen-ethyl, the end-use poduct and its major transformation products present a negligible risk to bees, birds and small mammals. However, pyraflufen-ethyl may affect some beneficial arthropods, terrestrial and aquatic plants, as well as amphibians.

In order to mitigate the potential effects of pyraflufen-ethyl to non-target organisms in terrestrial and aquatic habitats, instructions for spray buffer zones and reduction of run-off are required on the label.

7.3 Value

The information submitted is adequate to characterize the efficacy of NUP6D 04 Herbicide for control or suppression of emerged broadleaf weeds prior to the emergence of wheat (spring, durum, and winter), field corn, and soybean. A single application of NUP6D 04 Herbicide at 4.5 g a.i./ha with a NIS at 0.25% v/v provides control of lamb's-quarters and redroot pigweed and suppression of volunteer canola, dandelion, flixweed, wild buckwheat, kochia, and stinkweed. Efficacy information also indicated that NUP6D 04 Herbicide applied in a tank mix with a glyphosate herbicide (present as the isopropylamine or potassium salt) can be expected to control a broader spectrum of weeds.

Submitted information is also adequate to demonstrate that wheat (spring, durum, and winter), field corn, and soybean can be expected to exhibit an adequate margin of crop safety to a pre-emergence application of NUP6D 04 Herbicide at 4.5 g a.i./ha with a NIS at 0.25% v/v.

There are presently no documented cases of Weed Science Society of America Group 14 resistance of NUP6D 04 Herbicide labelled weeds in North America. However, there are documented cases of Group 14 resistance of other weeds in the U.S. As pyraflufen-ethyl belongs to a new chemical family, the phenylpyrazoles, within Group 14, NUP6D 04 Herbicide has the potential to contribute to the management of weeds that do not become cross-resistant to other Group 14 herbicides as well as to contribute to resistance management in the same manner as other Group 14 herbicides registered for pre-emergence use in wheat (spring, durum, and winter), soybean, and field corn.

The value of NUP6D 04 Herbicide relates to its potential contribution to herbicide resistance management as well as providing growers an additional weed control option within the Group 14 mode of action category.

8.0 Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, has granted conditional registration for the sale and use of Nufarm Pyraflufen-ethyl Technical and NUP6D 04 Herbicide, containing the technical grade active ingredient pyraflufen-ethyl, to be used on field corn, soybeans and wheat as preseed or pre-emergence application for broadleaf weed control in Canada.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

Although the risks and value have been found acceptable when all risk-reduction measures are followed, as a condition of these registrations, additional scientific information is being requested from the applicant. For more details, refer to the Section 12 Notice associated with these conditional registrations. The applicant will be required to submit this information within the time frames indicated below.

NOTE: The PMRA will publish a consultation document at the time when there is a proposed decision on applications to convert these conditional registrations to full registrations or on applications to renew the conditional registrations, whichever occurs first.

Environment

1. The applicant must submit the following information within two years of the registration decision.

    - To assess the potential bioaccumulation of the transformation product E-3 in fish, the applicant is to provide a bioaccumulation study in accordance with OECD guideline 305.

List of Abbreviations

♂	male
♀	female
ε (Lmol^{-1}cm^{-1})	molar absorption coefficient
λ	wavelength
μg	micrograms
8-OHdG	8-hydroxy-2'-deoxyguanosine
a.e.	acid equivalent
a.i.	active ingredient
abs	absolute
ACN	acetonitrile
AD	administered dose
ADI	acceptable daily intake
AFC	antibody forming cell
ALT	alanine aminotransferase
AR	Arkansas
AST	aspartate aminotransferase
atm	atmosphere
ATPD	area treated per day
AUC	Area Under Curve
BAF	Bioaccumulation Factor
BC	British Columbia
BCF	Bioconcentration Factor
bw	body weight
bwg	bodyweight gain
C_{max}	maximum concentration
Ca^{2+}	calcium ion
CA	California
CAF	composite assessment factor
CAS	Chemical Abstracts Service
Cl^-	chloride ion
cm	centimetres
COC	Crop oil concentrate
creat	creatinine
d	day(s)
DACO	Data Code
DALA	days after the last application
DAT	days after treatment
DEEM-FCID	Dietary Exposure Evaluation Model - Food Commodity Intake Database
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT_{90}	dissipation time 90% (the dose required to observe a 75% decline in concentration)
E-1	2-chloro-5-(4-chloro-5-difluoromethoxy-1-methylpyrazol-3-yl)-4-fluorophenoxyacetic acid

E-2	2-chloro-5-(4-chloro-5-difluoromethoxy-1-methylpyrazol-3-yl)-4-fluorophenol
E-3	4-chloro-3-(4-chloro-2-fluoro-5-methoxyphenyl)-5-difluoromethoxy-1-methylpyrazole
EC	emulsion concentrate
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
EC	emulsifiable concentrate
ECD	electron capture detector
EEC	estimated environmental concentration
EDE	estimated daily exposure
ELS	early life stage
EP	end-use product
EPSP	5-enolpyruvylshikimimate-3-phosphate
eq	equivalents
ER_{50}	effective rate for 50% of the population
ET-751	pyraflufen-ethyl; ethyl [2-chloro-5-(4-chloro-5-difluoromethoxy-1-methylpyrazol-3-yl)-4-fluorophenoxy]acetate
F_0	parental generation
F_1	first generation
F_2	second generation
fc	food consumption
fe	food efficiency
FIR	food ingestion rate
g	gram
GC	gas chromatography
GD	gestation day
GI	gastrointestinal
glc	glucose
GLP	good laboratory practice
GPA	gallons per acre
h	hour(s)
ha	hectare(s)
HAFT	highest average field trial
Hb	haemoglobin concentration
HCT	haematocrit
HD_5	hazardous dose to 5%
HPLC	high performance liquid chromatography
HR_5	hazardous rate to 5% (of species)
IA	Iowa
ID	Idaho
ICR	imprinting control region
IgM	immunoglobulin M
IL	Illinois
IN	Indiana
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram

K_d	soil-water partition coefficient
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
KS	Kansas
L	litre
LA	Louisiana
LADD	lifetime average daily dose
LAFT	lowest average field trial
LC_{50}	lethal concentration 50%
LC-MS/MS	liquid chromatography – tandem mass spectrometry
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOD	limit of detection
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
m	metre(s)
mg	milligram
mL	millilitre
m/z	mass-to-charge ratio of an ion
MAS	maximum average score
MBD	more balanced diet
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
MDA	malonyldialdehyde
MOA	mode of action
MOE	margin of exposure
MN	Minnesota
MRL	maximum residue limit
MS	mass spectrometry
MS/MS	tandem mass spectrometry
MT	moderately toxic
n	number of field trials
N/A	not applicable
NA	not available
NAFTA	North American Free Trade Agreement
NC	North Carolina
ND	North Dakota
NPD	nitrogen-phosphorous detector
NE	Nebraska
NIS	non-ionic surfactant
nm	nanometre
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NTP	National Toxicology Program

NZW	New Zealand white
OH	Ohio
OK	Oklahoma
ON	Ontario
Pa	pascals
PA	Pennsylvania
PBI	plantback interval
PCNA	proliferating cell nuclear antigen
pH	potential of hydrogen
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
p*K*a	dissociation constant
Plt	platelet
PMRA	Pest Management Regulatory Agency
PND	post-natal day
PNT	practically non-toxic
PPE	personal protective equipment
ppm	parts per million
PPO	protoporphyrinogen oxidase
q_1*	cancer potency factor
QC	Quebec
RBC	red blood cell
rel	relative
RNT	relatively non-toxic
RQ	risk quotient
SC	soluble concentrate
SD	standard deviation
SSD	Species sensitivity distribution
ST	slightly toxic
$t_{1/2}$	half-life
T_{max}	time to peak blood concentration
TG	triglyceride
TGAI	technical grade active ingredient
tot	total
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
TX	Texas
US	United States
USEPA	United States Environmental Protection Agency
UV	ultraviolet
v/v	volume per volume dilution
VHT	very highly toxic
WI	Wisconsin
wk	week(s)
wt/wts	weight/weights

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ		Reference
Plant	Not stated	ET-751 + E-1	GC-MS	0.02 ppm	cotton matrices (gin trash, seed hulls, meal and seed oil)	2130155
	Not stated	ET-751 + E-1	GC-MS/MS^1	0.020 mg/kg	cereal matrices (shoot, grain, processed products)	2130153
				0.040 mg/kg	cereal matrices (straw)	
	Not stated	ET-751	GC-NPD	0.010 mg/kg 0.020 mg/kg	wheat (grain) wheat (straw, shoot)	2130151
		E-1				
	Not stated	ET-751	GC-NPD	0.005 mg/kg	wheat grains	2130152
		E-1				
Animal	Not stated	ET-751 + E-1	GC-MS/MS^2	0.020 mg/kg	whole milk, beef muscle, liver and kidney, poultry liver and whole chicken egg	2130154
Soil	Not stated	ET-751	LC-MS/MS^3	0.002 mg/kg (LOD)		2130147
		E-1				
		E-2				
		E-3				
Sediment	The method used for soil was extended to sediment.					
Water	Not stated	E-1	LC-MS/MS^4	0.1 µg/L		2130148
	Not stated	ET-751	GC-ECD	0.1 µg/L	mineral and tap water	2130149
		E-1		1.0 µg/L	surface water	
Plant	ILSR-R95-024A	Pyraflufen-ethyl and E-1 (measured as E-15 and reported as pyraflufen-ethyl equivalents)	GC-NPD	0.01 (combined)	Wheat grain	PMRA# 2130151, 2130152
				0.02 (combined)	Wheat straw and shoots	
	AR165-98/98-66	Pyraflufen-ethyl and E-1 (measured as E-15 and reported as pyraflufen-ethyl equivalents)	GC-MS/MS; GC-MS	0.02 (combined)	Grain (wheat, barley, rye), shoots (wheat, barley, rye), rye meal and rye bran	PMRA# 2130153, 2130291
				0.04 (combined)	Straw (wheat, barley, rye)	
			GC-MSD	0.01 (combined)	Wheat grain	PMRA# 2130288
				0.02 (combined)	Wheat straw and shoots	
	831W* (Enforcement method)	Pyraflufen-ethyl and E-1 (measured as E-15 and reported as pyraflufen-ethyl equivalents)	GC-MS	0.02 (combined)	Cotton undelinted seed, gin trash, meal, hulls, oil; potato	PMRA# 2130155, 2130294
	A-5045	Pyraflufen-ethyl	GC-NPD	0.2 / 0.4	Citrus pulp / peel	PMRA# 2130150
	RCC A25986	Pyraflufen-ethyl; Metabolite E-1	HPLC-MS/MS	0.01 per analyte	Apple, pear, grape, oilseed rape	PMRA# 2130293
	Multiresidue method DFG S19	Pyraflufen-ethyl and metabolite E-1	LC-MS/MS	0.01 per analyte	Cucumber, wheat grain, orange, sunflower seed	PMRA# 2130287

Animal	AR158-97/97-183 (Enforcement method)	Pyraflufen-ethyl and E-1 (measured as E-15 and reported as pyraflufen-ethyl equivalents)	GC-MS/MS or GC-MS	0.02(combined)	Milk, beef muscle, liver, kidney, poultry muscle, eggs	PMRA# 2130154, 2130292, 2130309

[1] Transition ions: ET-751 412→349 m/z; E-1(methylated) 398→363 m/z

[2] Transition ions: ET-751 412→349 m/z; E-1(methylated) 398→363 m/z

[3] Transition ions: ET-751 413→339 m/z; E-1 383→325 m/z; E-2 327→277 m/z; E-3 341→291 m/z

[4] Transition ions: E-1 383→325 m/z

* The LOQ for Method 831W was determined as 0.005 ppm each for pyraflufen-ethyl and metabolite E-1, for a combined LOQ of 0.01 ppm, during concurrent method validation in the field corn, soybean and wheat field trials.

Table 2 **Toxicity Profile of Technical Pyraflufen-ethyl Technical**
(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted)

Study Type/Animal/PMRA #	Study Results
Toxicokinetic Studies	
Absorption, distribution, metabolism and elimination (ADME) Sprague-Dawley rats PMRA#2130136, 2130137, 2130138, 2130139	Both sexes were used: single 5 or 500 mg/kg oral dose low and high dose, or a 14-day repeated dose (5 mg/kg bw/day) using [pyrazole-5-^{14}C]-ET-751 and nonlabeled test article. Biliary excretion and metabolite profiles were assessed in males only given a single 5 mg/kg dose of [pyrazole-5-^{14}C] ET-751. A comparative metabolism and excretion study was also performed in both sexes using a single dose of [phenyl-U-^{14}C]-ET-751 at 5 mg/kg bw. There were no biologically significant treatment-related effects noted during the course of the study. ET-751 was readily absorbed (t_{max} at 3-4.5 h) at a concentration up to 2.75 µg-eq/g (C_{max}) and excreted within 24 hours following a single or repeated oral low dose. At the high dose, dose limited absorption occurred as C_{max} values did not reflect the 100-fold dose increase (~38-fold), but the exposure measured by the area under the curve (AUC) was closer to a 100-fold increase (76- to 85-fold). Urinary excretion was not affected by repeated dosing as the single and repeated low dose produced similar urinary excretion data, 27-33% of the administered dose (AD). At the high dose, urinary excretion was reduced to 5-7% of the AD. Excretion via the feces accounted for the remainder of the AD in all treatment groups. No excretion into the air was observed. Analysis of biliary excretion following a single low dose showed that ~36% of the AD appeared in the bile. Based upon the excretion data, total bioavailability at the low dose was ~56%. There was no gender-related difference regarding excretory patterns. The $t_{½\,elim}$ was 3 to 7 hours for all dose regimens. However, plasma and blood clearance was more rapid in females than in males as shown by plasma/blood radioactivity time course and the greater AUC values for males (1.75-fold at low dose and 1.95-fold at high dose). At 96 hr, radiolabelled tissue concentrations were all ≤ 0.02 µg-eq/g and generally close to the limit of detection. Highest concentrations of radiolabelled compound were recorded in the liver and kidneys. Metabolites were quantified and identified. The identified metabolites were

	consistent with phase 1 metabolism processes. The major metabolic pathway appears to be a sequential hydrolysis and demethylation of the parent compound to metabolites E-1 and E-9, the prominent components detected in the urine and faeces from all treatment groups.
Acute Toxicity Studies	
Acute oral toxicity ICR Mice PMRA #2130099	$LD_{50} > 5000$ mg/kg bw Low toxicity
Acute oral toxicity Sprague-Dawley rats PMRA #2130100	$LD_{50} > 5000$ mg/kg bw Low toxicity
Dermal toxicity Sprague-Dawley rats PMRA #2130101, 2130102	$LD_{50} > 2000$ mg/kg bw Low toxicity
Inhalation (nose-only) Sprague-Dawley rats PMRA #2130103	$LC_{50} > 5.03$ mg/L Low toxicity
Eye irritation Japanese White rabbits PMRA #2130104	MAS = 0.39/110 Minimally irritating
Dermal irritation Japanese White rabbits PMRA #2130105	MAS = 0/8 Non-irritating
Dermal sensitization (Maximisation Test) Hartley guinea pigs PMRA #2130107	Non-sensitizer
Short-Term Toxicity Studies	
28-day dietary toxicity ICR Mice	Range-finding **≥442/492 mg/kg bw/kg ♂/♀:** ↓ HCT, Hb and RBC count, ↑ Plt count, ↓ TG

PMRA #2158737	**1414/1682 mg/kg bw/day ♂/♀:** ↓ MCV, ↓ MCH, ↑ liver enzymes, ↑ tot bilirubin, ↓ glc, ↑ creat, ↑ Ca^{2+}, ↑ liver wt, enlarged liver, accentuated lobular pattern, dark coloured liver; ↑ spleen wt (♂); enlarged spleen (1♀)
28-day dietary toxicity Sprague-Dawley rats PMRA #2130110	Range-finding Mortality: 2619/2296 mg/kg bw/day: 2♂, 2♀ (week 2) **≥230.4 mg/kg bw/day ♂:** ↑ liver wt **2619/2296 mg/kg bw/day ♂/♀:** ↑ spleen wt, ↑ liver wt, pallor, ↓ fc, ↓ fe, polydipsia (wk 1), ↓ low packed cell volume, ↓ Hb, ↓ MCV, ↓ MCH, ↑leukocyte, ↑ reticulocyte, anisocytosis and hypochromasia, ↑ ALT, ↑ AST, ↑ cholesterol, ↑ bilirubin, ↓ Cl^-; ↓ MCHC, ↑ normoblast, ↓ myeloid:erythroid ratios, ↑ total protein, ↑ albumin, ↑ α-1 globulin, ↑ albumin: globulin ratio, ↑ rel kidney wt, swollen and/or enlarged spleens, ↑ incidence of extramedullary haematopoiesis (♂); ↓ urea (♀)
28-day dermal toxicity Sprague-Dawley rats PMRA #2130115	NOAEL= 1000 mg/kg bw/day No treatment-related effects
28-day oral toxicity (gavage) Beagle dogs PMRA #2158738	Range-finding No treatment-related effects up to 1000 mg/kg bw/day
90-day dietary toxicity Sprague-Dawley rats PMRA #2130110	NOAEL= 456 mg/kg bw/day LOAEL= 1489 mg/kg bw/day; based on mortality (3♂ ≤12 days), ↓ HCT, ↓ Hb, ↓ MCV, ↓ MCH, slight anisocytosis, spherocytosis, ↑ leukocytes and ↑ neutrophils and lymphocytes, ↑ spleen wt, ↓ tot protein, ↓ albumin; ↓ bw, ↓ bwg, ↑ liver enzymes, ↑ cholesterol, ↓ glc, ↓ α-1 globulin, ↑ β-globulin, ↑ rel kidney wt and rel spleen wt (♂) **Recovery study:** bwg back to control range, haematology changes still apparent after 3 weeks, neutrophil and lymphocyte numbers and tot leukocyte numbers marginally increased after 3 weeks and complete recovery after 5 weeks, organ wts were still elevated at the end of recovery period, recovery of the urinalysis parameters after 3 wks; partial recovery for MCV and MCH parameters at 5 weeks, recovery of packed cell volume and haemoglobin concentration after 7 weeks (♂) ; partial or complete haematology parameters recovery after 5 weeks (♀)

90-day oral toxicity (gavage) Beagle dogs PMRA #2130112	NOAEL= 1000 mg/kg bw/day No treatment-related effects
12-month oral toxicity (gavage) Beagle dogs PMRA #2130114	NOAEL= 1000 mg/kg bw/day No treatment-related effects
Chronic Toxicity/Oncogenicity Studies	
18-month oncogenicity (dietary) ICR mice PMRA #2130117	NOAEL= 21.0/19.6 mg/kg bw/day ♂/♀ LOAEL= 110/98 mg/kg bw/day ♂/♀; based on liver and kidney toxicity (spot(s) and masses in the liver, increased liver wts, hepatocellular vacuolation, micro-granuloma in liver, brown pigment deposition in cortico-medullary junction of the adrenal (♂ and ♀); coarse liver surface, focal hepatocellular necrosis and interstitial fibrosis, kidney cysts (♂); foci of cellular alteration (acidophilic and clear cell foci), brown pigment deposition in Kupffer cells, increased incidence of single cell necrosis, decreased spontaneous motor activity (♀) Oncogenicity Doses: 0, 21.0/19.6, 110/98, 547/524 mg/kg bw/day for ♂/♀ Hepatocellular adenomas at terminal sacrifice (♂/♀): (16/1, 12/0, 24^{*}/1, 31^{**}/16^{**}) n=41-48 Hepatocellular carcinomas at terminal sacrifice (♂/♀): (1/0, 1/0, 2/0, 1/1) n=41-48 Hepatoblastomas at terminal sacrifice (♂/♀): (0/0, 0/0, 1/0, 1/0) n=44-48 Combined adenomas/carcinomas/hepatoblastomas (♂/♀): (17/1, 12/0, 25^{*}/1, 33^{**}/16^{**}) n=41-48 *, **: Significantly different from the control at 5% (*) or 1% (**) level of probability Evidence of oncogenicity
2-year combined chronic/oncogenicity (dietary) Sprague-Dawley rats PMRA# 2130120, 2130121, 2130122	NOAEL= 87/112 mg/kg bw/day LOAEL= 468/579 mg/kg bw/day; based on kidney toxicity (hyperplasia, papillary transitional hyperplasia, papillary necrosis/sloughing, acute papillitis, dilation/hyperplasia of collecting ducts, acute pyelitis, dilated cortical tubules, cortical cysts in ♂ and ♀) and liver toxicity (bile duct hyperplasia [♂ and ♀], focal inflammation with hepatocytes degeneration, periacinar hepatocytes fatty vacuolation and hypertrophy, periacinar hepatocytes (♂) and microcytic anemia (♀)) No evidence of oncogenicity

Developmental/Reproductive Toxicity Studies	
1-Generation Dietary Reproductive Toxicity (range-finding) (diet) Sprague-Dawley rats PMRA #2130123	Range-finding **Parental Toxicity** **669/765 mg/kg bw/day** ♂/♀**:** ↑ incidence of dark liver and kidney, ↓ abs spleen wt; ↓ bw (from wk 2 until termination), ↓ fc (from wk 1), ↓ abs liver wt (♂) **Offspring Toxicity** **669/765 mg/kg bw/day** ♂/♀**:** ↓ bw during lactation **Reproductive Toxicity** **669/765 mg/kg bw/day** ♂/♀**:** 1 complete litter resorption
2-Generation Dietary Reproductive Toxicity (diet) Sprague-Dawley rats PMRA #2130123, 2130124	**Parental Toxicity** NOAEL = 70.8/80.1 mg/kg bw/day ♂/♀ LOAEL = 721-844/813-901 mg/kg bw/day ♂/♀: ↑ fc (F_0 premating), ↓ bw (F_1), ↓ bwg (F_1), ↓ fc (F_1 premating), ↑ incidence of dark coloured liver (F_0 and F_1) and kidney (F_0 and F_1), ↑ kidney wt (F_0 and F_1), ↓ adrenal wt (F_1), ↑ incidence of liver single cell necrosis (F_0 and F_1) and inflammatory cell infiltration (F_0 and F_1), ↑ incidence of pigment deposition in liver (F_0 and F_1), ↑ incidence of pigment deposition in the kidney (F_0 and F_1); ↓ bw (F_0) premating until termination), ↓ bwg (F_0 premating), ↓ abs liver wt (F_0), ↑ incidence of bile duct proliferation (F_0 and F_1), ↑ incidence of centrilobular hepatocellular swelling (F_1), ↑ loss of acidophilic body in proximal tubule (F_0 and F_1) (♂); ↑ liver wt (F_0), ↑ rel liver wt (F_1) (♀) **Offspring Toxicity** NOAEL = 70.8/80.1 mg/kg bw/day ♂/♀ LOAEL = 721-844/813-901 mg/kg bw/day ♂/♀: ↓ bw (F_1; and F_2 PND 21]), ↓ bwg (F_1 and F_2 at PND 7-21); ↓ bw (F_2 at PND 14) (♀) **Reproductive Toxicity** NOAEL = 721/813 mg/kg bw/day ♂/♀ (highest dose tested) LOAEL = not determined **No evidence of sensitivity of the young**
Developmental toxicity (gavage) Sprague-Dawley rats PMRA #2130126	Range-finding **Maternal** No treatment-related effects at the limit dose. **Developmental** No treatment-related effects at the limit dose.

Developmental toxicity (gavage) Sprague-Dawley rats PMRA #2130125	**Maternal** NOAEL = 1000 mg/kg bw/day LOAEL = not determined. No treatment-related effects at the limit dose. **Developmental** NOAEL = 1000 mg/kg bw/day LOAEL = not determined. No treatment-related effects at the limit dose. **No evidence of sensitivity of the young** **No evidence of malformations**
Developmental toxicity (gavage) NZW rabbits PMRA #2130128	Range-finding study **Maternal** **200 mg/kg bw/day:** transient body weight loss (GDs 1-4), ↓ fc, agonal signs and death (1 dam at GD 19) **400 mg/kg bw/day:** agonal signs and deaths (4 dams at GDs 11-17) **Developmental** **≥100 mg/kg bw/day:** ↓ bw
Developmental toxicity (gavage) NZW rabbits PMRA #2158739	**Maternal** NOAEL = 20 mg/kg bw/day LOAEL = 60 mg/kg bw/day: agonal signs and deaths (3 dams at GD 19), GI tract lesions **Developmental** NOAEL = 60 mg/kg bw/day LOAEL = 150 mg/kg bw/day: abortions (3 at GDs 17-20) **No evidence of sensitivity of the young** **No evidence of malformations**
Neurotoxicity Studies	
Acute Neurotoxicity Sprague-Dawley Rats PMRA #1218719, 2340649	NOAEL = 2000/500 mg/kg bw ♂/♀ LOAEL = not determined/2000 mg/kg bw ♂/♀: ↓ bwg during wk 1 (♀) **No neurotoxicity**
90-day Neurotoxicity (dietary) PMRA #2328720, 2340650	NOAEL = 61/222 mg/kg bw/day ♂/♀ LOAEL = 174/625 mg/kg bw/day ♂/♀: ↓ bwg during wk 1 (♂); anemia (♀) **No neurotoxicity**
Genotoxicity Studies	

Gene Mutation in Bacteria *Salmonella typhimurium* (TA1535, TA1537, TA1538, TA98, TA100) *E. coli* (WP2[uvrA]) PMRA #2130129	Negative
In vivo mammalian micronucleus assay CD-1 mice PMRA #2130131	Negative
Gene Mutation in Mammalian cells in vitro TK locus, L5178Y mouse lymphoma cultured cells PMRA #2130133	Negative
Chromosome aberration in vitro Bacterial strains H17 (rec+) and M45 (rec-) of *B. subtilis* PMRA #2130134	Negative
Unscheduled DNA synthesis in vivo Rat hepatocytes cultured from F344 rat PMRA #2130135	Negative
Metabolite Studies	
ET-751 carboxylic acid metabolite; 2-Chloro-5-(4-chloro-5-difluoromethoxy-1-methylpyrazol-3-yl)-4-fluorophenoxyacetic acid (E-1)	
Acute oral toxicity Sprague-Dawley rats PMRA # 2130108	$LD_{50♂}$ greater than 1000 mg/kg bw, but less than 3000 mg/kg bw $LD_{50♀} \geq 3000$ mg/kg bw Slight toxicity
Special Studies	

Immunotoxicity (diet) Sprague-Dawley rats PMRA #2130140	NOAEL = 236/1114 mg/kg bw/day ♂/♀ **943 mg/kg bw/day ♂:** ↓ IgM antibody-forming cell (AFC) response, ↓ total spleen activity, ↓ bw, ↓ bwg, ↓ fc, ↓ fe, ↓ abs spleen wt
Special Studies (non-guideline)	
Tolerance study (gavage) Staircase study NZW rabbits PMRA #2158736	Staircase study: **800 mg/kg bw/day:** ↓ bw Continuation study: **600 mg/kg bw/day:** ↓ bw, both dams were found death (GDs 11 and 13), dark depressions on the internal stomach wall, disturbance of the GI tract, dark red urine in urinary bladder, signs of early resorption **Conclusions:** highest dosage for use in a preliminary teratology study in the rabbit should be in the region of 400 mg/kg bw/day.
Microscopic Liver Injury (diet) ICR mice PMRA #2130116	Concentration of 10000 ppm was lethal (≤9 days), whereas concentrations of 3000 ppm and 5000 ppm were not lethal, but increased the serum AST (2.4- to 2.5-fold after 2 wks) and ALT (8.1- to 9.2-fold after 4 wks) activities and induced liver toxicity manifested by a variety of lesions including hepatocellular necrosis and cell proliferation; neither hepatocellular necrosis nor cell proliferation corresponded with the increases in serum AST or ALT activities.
Study on effect on proliferative activity of hepatic cells (diet) ICR mice PMRA #2130118	Measurement of the proliferative activity of hepatocytes by immunohistochemical staining for proliferating cell nuclear antigen (PCNA) in liver sections from mouse dietary oncogenicity study (PMRA# 2130117) at 13 and 78 weeks. At 13 weeks: **≥110/98 mg/kg bw/day:** ↑ hepatocyte proliferative activity At 78 weeks: **≥110/98 mg/kg bw/day:** ↑ hepatocyte proliferative activity
Study on porphyrin accumulation in the liver (diet) ICR mice PMRA #2130119	Performed to clarify if porphyrin is contained within the brown pigment granules deposited in the liver (Kupffer cells) observed at the mid- and high dose groups in the mouse dietary oncogenicity study (PMRA# 2130117). The staining profile of the Kupffer cells is compatible with the presence of polysaccharide, lipofuscin, and porphyrin.

Hepatic drug metabolizing enzymes study ICR Mice PMRA #2340645	Enzyme activity of ethoxyresorfin O-dealkylase (CYP2B/2), pentoxyresorfin O-dealkylase (CYP1A1), ethoxycoumarin O-deethylase (CYP1A1/2), aniline dehydroxylase, and aminopyrine N-demethylase were measured. Phenobarbital was used as positive control. **Conclusion:** No elevation of activity was observed in the selected enzymes.
Effect pyraflufen-ethyl on lipid peroxidation, β-oxidation activity, catalase activity and 8-hydroxyguanosine production for 7 days ICR Mice PMRA #2340648	**5000 ppm:** ↑ abs and rel liver wt (↑ 39% and 46%), ↑ β-oxidation activity (↑ 367%), ↓ catalase activity (↓ 86%) **≥5000 ppm:** ↑ MDA (↑ 220%) **10000 ppm:** ↓ bw (↓ 25%), ↑ 8-OHdG (↑ 79%) **Conclusion:** This study confirmed the ability of a 7-day treatment with pyraflufen-ethyl to induced lipid peroxidation at doses ≥5000 ppm. (equivalency in mg/kg bw/day not reported)

Table 3 Toxicity Profile of NUP6D 04 Herbicide Containing 2.5% w/w Pyraflufen-ethyl Technical

Study Type/Animal/PMRA #	Study Results
Acute oral toxicity Sprague-Dawley rats PMRA #2130268	LD_{50}♂ = 5000 mg/kg bw ♀ = 3712 mg/kg bw Combined = 4238 mg/kg bw Low toxicity
Acute dermal toxicity Sprague-Dawley rats PMRA #2130269	LD_{50} > 2000 mg/kg bw Low toxicity
Acute inhalation toxicity (nose-only) Sprague-Dawley rats PMRA #1230270	LC_{50} > 2.03 mg/L Low toxicity

Dermal irritation Japanese White rabbits PMRA #2130272	MAS = 7.3/8 Extremely irritating
Eye irritation NZW rabbits PMRA #2130271	MAS = 32.8/110 Mean irritation score greater than 10/110 at 7 days and unresolved irritation after 21 days Severely irritating
Dermal sensitization (Buehler Test) Guinea pigs PMRA #2328724	Non-sensitizer

Table 4 Toxicology Endpoints for Use in Health Risk Assessment for Pyraflufen-ethyl

Exposure Scenario	Study	Point of Departure and Endpoint		CAF[1] or Target MOE
Acute dietary	No acute endpoints of concern were identified			
	Acute reference dose = N/A			
Repeated dietary	Mouse dietary oncogenicity	NOAEL = 20 mg/kg bw/day	Liver toxicity at LOAEL of 98 mg/kg bw/day	100
	Developmental oral toxicity rabbit study (maternal toxicity)		Deaths, GI tract lesions and body weight effects at LOAEL of 60 mg/kg bw/day	
	Acceptable daily intake = 0.2 mg/kg bw/day			
Inhalation[2] (short- and intermediate-term)	Developmental oral toxicity rabbit study (maternal toxicity)	NOAEL= 20 mg/kg bw/day Deaths, GI tract lesions and body weight effects at LOAEL of 60 mg/kg bw/day		100
Dermal (short- and intermediate-term)	28-day dermal toxicity study in rats	NOAEL= 1000 mg/kg bw/day Highest dose tested, no adverse effects.		100
Cancer	$q_1^* = 1.57 \times 10^{-2}$ (mg/kg bw/day)$^{-1}$ {male mice combined hepatocellular adenomas, hepatocellular carcinomas and hepatoblastomas}			

Table 5 Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUE IN WHEAT	**PMRA# 2130143**
Radiolabel Position	[5-pyrazole-^{14}C]-PFE and [phenyl-U-^{14}C]-PFE
Test Site	1 m^2 field plots with netting
Treatment	Foliar treatment using a hand-sprayer
Total Rate	Single application at 20 g a.i./ha; to immature wheat plants at the ~4-leaf growth stage
Formulation	Suspension concentrate (SC) formulation
Preharvest interval	23 days for forage, 84 days for grain, chaff, straw

Matrices	**PHI (days)**	**[5-pyrazole-^{14}C]-PFE**	**[phenyl-U-^{14}C]-PFE**
		TRRs (ppm)	**TRRs (ppm)**
Forage	23	0.031	0.038
Grain	84	0.0002	0.0002
Chaff	84	0.0019	0.0027
Straw	84	0.0198	0.0145
Soil (1 day)	1	0.0104 - 0.0122	0.0086 - 0.0123
Soil (23 days)	23	0.0146	0.0156
Soil (84 days)	84	0.0141	0.0157

Metabolites Identified	**Major Metabolites (>10% of the TRRs)**		**Minor Metabolites (<10% of the TRRs)**	
Radiolabel Position	**[5-pyrazole-^{14}C]**	**[phenyl-U-^{14}C]**	**[5-pyrazole-^{14}C]**	**[phenyl-U-^{14}C]**
Forage	PFE, E-1	PFE	E-9	E-1, E-9
Straw	E-1	E-1	E-2, E-3, E-9	E-2, E-3, E-9
Soil (1 day)	PFE, E-1	PFE, E-1	E-2, E-4	E-2, E-4
Soil (23 days)	E-1, E-2, E-3, E-4	E-1, E-2, E-3, E-4	PFE, E-9	PFE, E-9
Soil (84 days)	E-2, E-3	E-2, E-3	PFE, E-1, E-4, E-9	PFE, E-1, E-4, E-9

Grain and chaff were not included because the TRRs did not warrant metabolite identification.

NATURE OF THE RESIDUE IN POTATO	**PMRA# 2130145**
Radiolabel Position	[5-pyrazole-^{14}C]-PFE and [phenyl-U-^{14}C]-PFE
Test Site	4' × 8' field plots surrounded by wire mesh
Treatment	Foliar treatment using a single-nozzle CO$_2$ sprayer
Total Rate	Single application at 34.7 g a.i./ha; to mature potato plants
Formulation	Pyrazole-labeled test substance was diluted with ACN; acetone was added to dissolve the precipitate that formed; phenyl-labeled test substance was diluted in ACN:water (50:50)
Preharvest interval	7 days

Matrices	**PHI (days)**	**[5-pyrazole-^{14}C]-PFE**	**[phenyl-U-^{14}C]-PFE**
		TRRs (ppm)	**TRRs (ppm)**
Tubers (whole potato tuber including peel)	7	0.0009	0.0009
Peel	7	0.001	0.0003
Leaves	7	6.535	7.052

Metabolites Identified	**Major Metabolites (>10% of the TRRs)**		**Minor Metabolites (<10% of the TRRs)**	
Radiolabel Position	**[5-pyrazole-^{14}C]**	**[phenyl-U-^{14}C]**	**[5-pyrazole-^{14}C]**	**[phenyl-U-^{14}C]**
Tubers	E-1	None	PFE, E-9	E-1, E-9
Leaves	PFE	PFE, E-1	E-1	E-9

NATURE OF THE RESIDUE IN COTTON	**PMRA# 2130146**
Radiolabel Position	[5-pyrazole-^{14}C]-PFE and [phenyl-U-^{14}C]-PFE
Test Site	4' × 8' field plots surrounded by wire mesh
Treatment	Foliar treatment using a single-nozzle CO_2 sprayer
Total Rate	Single application at 5.6 g a.i./ha; at 60-70% boll opening stage
Formulation	Test substances were diluted with ACN and water
Preharvest interval	7 days

Matrices	**PHI (days)**	**[5-pyrazole-^{14}C]-PFE**	**[phenyl-U-^{14}C]-PFE**
		TRRs (ppm)	**TRRs (ppm)**
Composite gin byproducts	7	0.283	0.232
Field gin byproducts	7	0.476	0.212
Seed kernel	7	<0.00005	0.0006
Seed lint/hulls	7	0.001	0.0005

Metabolites Identified	**Major Metabolites (>10% of the TRRs)**		**Minor Metabolites (<10% of the TRRs)**	
Radiolabel Position	**[5-pyrazole-^{14}C]**	**[phenyl-U-^{14}C]**	**[5-pyrazole-^{14}C]**	**[phenyl-U-^{14}C]**
Gin byproducts	PFE, E-1	PFE, E-1	E-2, E-9	E-2, E-9
Seed lint/hulls	PFE	PFE	None	E-9

NATURE OF THE RESIDUE IN MANDARIN ORANGE	**PMRA# 2130144 and 2220407**
Radiolabel Position	[5-pyrazole-^{14}C]-PFE
Test Site	20 cm pots under greenhouse conditions
Treatment	Soil-surface treatment using a pipette
Total Rate	Single application at 15.57 kg a.i./ha (1.56 g a.i./m^2)
Formulation	Emulsion concentrate (EC) formulation
Preharvest interval	0, 28 and 61 days

Matrices	**PHI (days)**	**[5-pyrazole-^{14}C]-PFE**
		TRRs (ppm)
Fruit, pulp	0	<0.0001, <0.0001
	28	<0.0001, <0.0001
	61	<0.0001, <0.0001
Fruit, peel	0	<0.0003, <0.0003
	28	<0.0003, <0.0003
	61	<0.0003, <0.0003
Leaves	0	<0.0003, <0.0003
	28	0.0004, <0.0003
	61	0.0016, 0.00038
Tree trunk – 3 cm above ground	0	<0.0002, <0.0002
	28	0.00014, <0.0002
	61	0.00055, <0.0002
Tree trunk – 10 cm above ground	0	<0.0002, <0.0002
	28	<0.0002, <0.0002
	61	0.00035, 0.00018

Roots	0	0.00735, 0.00239
	28	0.00239, 0.00108
	61	0.00412, 0.00076

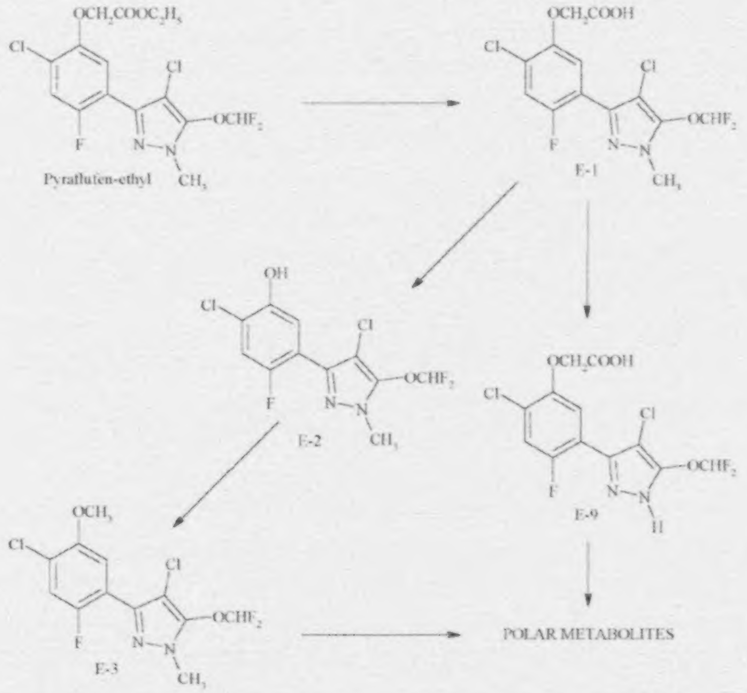
Metabolites Identified	**Major Metabolites (>10% of the TRRs)**	**Minor Metabolites (<10% of the TRRs)**
Radiolabel Position	**[5-pyrazole-^{14}C]**	**[5-pyrazole-^{14}C]**
Soil (61 DAT), 0-3 cm	E-1, E-3	PFE, E-2, E-9, E-10, E-11
Soil (61 DAT), 3-10 cm	None	PFE, E-1, E-2, E-3, E-8, E-9, E-10, E-11
Soil (61 DAT), 10 cm	None	PFE, E-1, E-2, E-3, E-9, E-10, E-11
Soil (61 DAT), **Total**	E-1, E-3	PFE, E-2, E-8, E-9, E-10, E-11

CONFINED ACCUMULATION IN ROTATIONAL CROPS – Radish, lettuce and barley	**PMRA# 2130306**
Radiolabel Position	[5-pyrazole-^{14}C]-PFE
Test site	Individual containment vessels filled with soil and set in the ground
Formulation	Test substance was dissolved in ethanol
Application rate and timing	Bare soil was treated at 14.2 g a.i./ha, and aged for 30, 120/150 days.

Metabolites Identified		**Major Metabolites (>10% of the TRRs)**	**Minor Metabolites (<10% of the TRRs)**
Matrices	**PBI (days)**	**[5-pyrazole-^{14}C]-PFE**	**[5-pyrazole-^{14}C]-PFE**
Radish Tops (TRRs=0.001 ppm)	30	Polar, Aqueous	E-1, E-2, E-3
Barley Straw (TRRs=0.003 ppm)	30	Polar	Unknowns 1 (polar), 2 (nonpolar) and 3 (nonpolar)

Proposed Metabolic Scheme in Plants

The proposed metabolic pathway for pyraflufen-ethyl in plants mainly involves ester hydrolysis to form the acid metabolite E-1 and demethylation of the pyrazole ring to form the desmethyl metabolite E-9. In soil samples from the wheat study and in wheat straw, further metabolism of the phenoxyacetate group yielding the phenolic metabolite E-2, and methoxylation to yield metabolite E-3 was observed. The remaining metabolites are expected to be polar in nature.



NATURE OF THE RESIDUE IN LAYING HEN | **PMRA# 2130141**

Six laying hens were dosed orally with [^{14}C]pyraflufen-ethyl labeled at the 5-position of the pyrazole ring, at 10.5 ppm once daily for 3 consecutive days. Eggs were collected twice daily. Excreta were collected twice daily and composited. The hens were sacrificed 22-23 hours following the final dose, and the following samples were collected: entire liver, composite muscle (breast and thigh), mesenteric fat, and GI tract (with contents). A control group of six hens was included in the study.

Matrices	**5-pyrazole-^{14}C-PFE**	
	TRRs (ppm)	**% of Administered Dose**
Excreta (including cage wash)	--	90.2
GI Tract		0.2
Muscle	<0.001	<0.1
Fat	≤0.001	<0.1
Liver	0.019	<0.1
Egg whites (0-24 h)	<0.001	<0.1
Egg whites (24-48 h)	<0.001	<0.1
Egg whites (48 h-sacrifice)	≤0.003	<0.1
Egg yolks (0-24 h)	<0.002	<0.1
Egg yolks (24-48 h)	<0.002	<0.1
Egg yolks (48 h-sacrifice)	0.004	<0.1

Metabolites identified	Major Metabolites (>10% of the TRRs)	Minor Metabolites (<10% of the TRRs)
Radiolabel Position	**5-pyrazole-^{14}C-PFE**	**5-pyrazole-^{14}C-PFE**
Liver	E-1, E-9	None
Egg whites (48 h-sacrifice)	E-1, E-9	None
Egg yolks (48 h-sacrifice)	E-1, E-9	None

Muscle and fat were not included because the TRRs did not warrant metabolite identification.

NATURE OF THE RESIDUE IN LACTATING GOAT	PMRA# 2130142

A single lactating goat was dosed orally with [^{14}C]pyraflufen-ethyl labeled at the 5-position of the pyrazole ring, at 10 ppm once daily for 3 consecutive days. Samples of urine were collected once daily; samples of feces and milk were collected twice daily. The goat was sacrificed 23 hours following the final dose, and the following samples were collected: entire liver, both kidneys, composite muscle (loin and hind-quarter), composite fat (perirenal and omental), and GI tract (with contents). A control goat was included in the study.

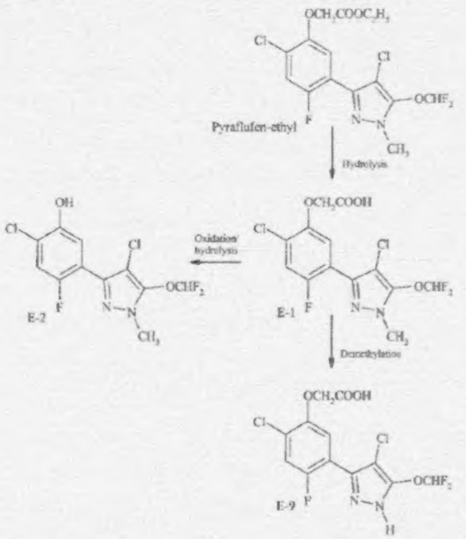
Matrices	5-pyrazole-^{14}C-PFE	
	TRRs (ppm)	**% of Administered Dose**
Urine (including cage wash)	--	39.6
Feces (including cage solids and bile)	--	30.7
Blood	0.011	<0.1
Muscle	<0.001	<0.1
Fat	0.003	<0.1
Kidney	0.079	<0.1
Liver	0.047	0.1
Milk (0-8 h)	0.019	0.02
Milk (8-24 h)	0.009	0.02
Milk (24-32 h)	0.025	0.03
Milk (32-48 h)	0.012	0.02
Milk (48-56 h)	0.017	0.02
Milk (56 h-sacrifice)	0.014	0.03

Metabolites identified	Major Metabolites (>10% of the TRRs)	Minor Metabolites (<10% of the TRRs)
Radiolabel Position	**5-pyrazole-^{14}C-PFE**	**5-pyrazole-^{14}C-PFE**
Kidney	E-1	E-2, E-9
Liver	E-1	E-2, E-9
Milk (0-8 h)	E-1, E-9	None
Milk (8-24 h)	E-1, E-9	None
Milk (24-32 h)	E-1, E-9	None
Milk (32-48 h)	E-1, E-9	None
Milk (48-56 h)	E-1, E-9	None
Milk (56 h -sacrifice)	E-1, E-9	None

Muscle and fat were not included because the TRRs did not warrant metabolite identification.

Proposed Metabolic Scheme in Livestock

The proposed metabolic pathway for pyraflufen-ethyl in animals mainly involves ester hydrolysis to form the carboxylic acid derivative E-1 and the phenolic derivative E-2, and demethylation to form the desmethyl derivative of E-1 (metabolite E-9).



FREEZER STORAGE STABILITY	**PMRA# 2130297, 2130298, 2130155, 2222193 and 2130309**

Plant matrices: The freezer storage stability data indicate that combined residues of pyraflufen-ethyl and E-1 are stable when stored at -20°C for up to 187 days (6.2 months) in **cotton seed**, 201 days (6.6 months) in **cotton gin byproducts**, 70 days (2.3 months) in **cotton hulls**, 63 days (2.1 months) in **cotton meal**, 71 days (2.3 months) in **refined cotton oil**, 127 days (4.2 months) in **corn forage, stover and grain**, 177 days (5.8 months) in **soybean forage, hay and seed**, 1324 days (3.6 years) in **wheat forage and hay**, 397 days (13 months) in **wheat grain**, and 510 days (17 months) in **wheat straw**. Conversion of pyraflufen-ethyl to metabolite E-1 was observed in corn forage and stover, and wheat forage, hay and grain, as indicated by low recoveries of pyraflufen-ethyl (<70%) after storage, and corresponding high recoveries for E-1 (>135%), where the recoveries for combined residues were 86-111%.

Animal matrices: The freezer storage stability data indicate that combined residues of pyraflufen-ethyl and E-1 are stable when stored at -20°C for up to 59 days in **liver and kidney**, 78 days in **muscle and fat**, and 102 days in **milk**. Conversion of pyraflufen-ethyl to metabolite E-1 was observed in liver and kidney, as indicated by low recoveries of pyraflufen-ethyl (<67%) after storage, and corresponding high recoveries for E-1 (>113%), where the recoveries for combined residues were 93-112%.

CROP FIELD TRIALS & RESIDUE DECLINE ON SOYBEAN	**PMRA# 2130308 and 2130304**

Preplant treatment: Three field trials were conducted in the US in Regions 2 (1 trial; NC), 5 (1 trial; IL), and 10 (1 trial; CA) during the 2000 growing season. The 20 g/L soluble concentrate (SC) formulation of pyraflufen-ethyl was applied in all three test sites; in addition, the 25 g/L emulsifiable concentrate (EC) formulation was applied in the NC test site. These formulations were applied as a single broadcast soil application at 10.1-10.5 g a.i./ha, prior to soybean planting. The spray mixture was applied at 213-343 L/ha (19.0-30.5 GPA). Adjuvant use was not specified. Soybean forage samples were collected when the soybeans were at least eight inches tall but not later than the beginning of pod formation, at preharvest intervals (PHIs) of 44-69 days; hay samples were cut when the soybeans were at mid-to-full bloom but prior to 50% pod development, at PHIs of 44-84 days. Hay samples were allowed to dry for 3-26 days to reach a moisture content of ~10-20% (80-90% dry matter). Soybean seed samples were harvested at commercial maturity, at PHIs of 121-140 days.

Preplant + postemergence treatment: Twenty soybean field trials were conducted in the US in Regions 2 (NC and SC; 2 trials), 4 (AR and LA, 3 trials), and 5 (IA, IL, IN, MN, NE, and OH; 15 trials) during the 2005 growing season. In each test, a 25 g a.i./L emulsifiable concentrate (EC) formulation of pyraflufen-ethyl was applied to soybeans as a combined preplant broadcast application and postemergence broadcast foliar spray at 1.8 g a.i./ha/application, at retreatment intervals of 33-87 days, for a total of 3.6 g a.i./ha/season. Applications were made using ground equipment in volumes of 47-191 L/ha, and did not include the use of any adjuvants. Data from the two residue decline tests indicated that residues of both pyraflufen-ethyl and E-1 declined in soybean forage and hay at longer post-treatment intervals. As residues of both analytes were not detected in/on any seed samples, no pattern of decline could be determined for seeds.

Commodity	Total Application Rate/ Method (g a.i./ha)	PHI (days)	Residue Levels (ppm)							
			n	Min#	Max#	LAFT*	HAFT*	Median*	Mean*	SD*
Combined residues of pyraflufen-ethyl and metabolite E-1										
Soybean forage	10.1 g a.i./ha (preplant; SC)	44-69	3	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A
Soybean hay		44-84	3	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A
Soybean seed		121-140	3	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A
Soybean forage	10.1 g a.i./ha (preplant; EC)	54	1	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A
Soybean hay		84	1	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A
Soybean seed		140	1	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A
Soybean forage	1.8 g a.i./ha (preplant) + 1.8 g a.i./ha (postemergence)	6-7	20	<0.01	0.042	<0.01	0.042	0.014	0.018	0.008
Soybean hay		6-7	20	<0.01	0.086	<0.01	0.084	0.024	0.032	0.020
Soybean seed		64-105	20	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A

Values based on total number of samples.

* Values based on per-trial averages. LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard Deviation. For computation of the LAFT, HAFT, median, mean and standard deviation, values <LOQ are assumed to be at the LOQ.

n = number of field trials.

CROP FIELD TRIALS & RESIDUE DECLINE ON FIELD CORN — **PMRA# 2130300, 2222187 and 2130303**

Preplant treatment: Three field trials were conducted in the US in Regions 2 (1 trial; NC), 5 (1 trial; IL), and 10 (1 trial; CA) during the 2000 growing season. The 20 g/L soluble concentrate (SC) formulation of pyraflufen-ethyl was applied in all three test sites; in addition, the 25 g/L emulsifiable concentrate (EC) formulation was applied in the NC test site. These formulations were applied as a single broadcast soil application at 9.8-10.4 g a.i./ha, prior to corn planting. The spray mixture was applied at 213-348 L/ha (19-31 GPA). Adjuvant use was not specified. Field corn forage samples were harvested at the late dough/early dent stage, at preharvest intervals (PHIs) of 97-98 days; grain and stover samples were harvested at commercial maturity, at PHIs of 140-152 days.

Preplant + postemergence treatment: Twenty field corn field trials were conducted in the US in Regions 1 (PA; 1 trial), 2 (NC; 1 trial), 5 (IA, IL, IN, MN, NE, OH, and WI; 16 trials), 6 (TX, 1 trial), and 7 (NE, 1 trial) during the 2005 growing season. In nineteen of the twenty tests, a 25 g a.i./L emulsifiable concentrate (EC) formulation of pyraflufen-ethyl was applied to field corn as a combined preplant broadcast application and postemergence broadcast foliar spray at 1.8-2.0 g a.i./ha/application, at retreatment intervals of 40-56 days, for a total of 3.6-3.8 g a.i./ha/season. Due to application errors, only a single postemergence foliar application at 1.8 g a.i./ha was made at one of the trials conducted in Zone 5 (Trial ID TCI-05-114-06). Postemergence applications were made at approximately the 7- to 8-leaf stage. Applications were made using ground equipment in volumes of 47-191 L/ha, and did not include the use of any adjuvants. Duplicate treated samples of corn forage were collected 47-79 days after the last application (DALA) when the field corn was at the dough/early dent stage, and duplicate grain and stover samples were collected at normal crop maturity, 86-120 DALA. As no residues were detected in any of the samples from the decline trials, residue decline could not be determined.

Commodity	Total Application Rate/ Method (g a.i./ha)	PHI (days)	Residue Levels (ppm)							
			n	Min#	Max#	LAFT*	HAFT*	Median*	Mean*	SD*
Combined residues of pyraflufen-ethyl and metabolite E-1										
Corn forage	10.1 g a.i./ha (preplant; SC)	97-98	3	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A
Corn grain		140-152	3	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A
Corn stover		140-152	3	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A
Corn forage	10.1 g a.i./ha (preplant; EC)	97	1	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A
Corn grain		140	1	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A
Corn stover		140	1	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A
Corn forage	1.8-1.9 g a.i./ha (preplant) +	47-79	19	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A
Corn grain		86-120	19	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A

Corn stover	1.8-1.9 g a.i./ha (postemergence)	86-120	19	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A

[#] Values based on total number of samples.

[*] Values based on per-trial averages. LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard Deviation. For computation of the LAFT, HAFT, median, mean and standard deviation, values <LOQ are assumed to be at the LOQ.

n = number of field trials.

CROP FIELD TRIALS & RESIDUE DECLINE ON WHEAT — PMRA# 2222169 and 2130301

Preplant treatment: Three field trials were conducted in the US in Regions 2 (1 trial on winter wheat; NC), 5 (1 trial on spring wheat; ND), and 10 (1 trial on winter wheat; CA) during the 2000 growing season. The 20 g/L soluble concentrate (SC) formulation of pyraflufen-ethyl was applied in all three test sites; in addition, the 25 g/L emulsifiable concentrate (EC) formulation was applied in the NC test site. These formulations were applied as a single broadcast soil application at 9.7-10.1 g a.i./ha, prior to wheat planting. The spray mixture was applied at 207-231 L/ha (18.4-20.6 GPA). Adjuvant use was not specified. Wheat forage samples were collected when the wheat was at least six to eight inches tall but prior to the stem elongation (jointing) stage, at preharvest intervals (PHIs) of 28-153 days; hay samples were cut when the wheat was at least at early flower (boot) stage but prior to the soft dough stage, at PHIs of 50-212 days. Hay samples were allowed to dry for 6-24 days to reach a moisture content of ~16-29%. Wheat grain and straw samples were harvested at commercial maturity, at PHIs of 96-225 days.

Preplant + postemergence treatment: Twenty wheat field trials were conducted in the US in Regions 2 (NC; 1 trial), 4 (AR; 1 trial), 5 (IL, KS, MN, NE, and OH; 5 trials), 6 (TX; 1 trial), 7 (ND and NE; 5 trials), 8 (KS, OK, and TX; 6 trials), and 11 (ID; 1 trial) during the 2005 growing season. Eight of the field trials used spring wheat, and the remaining 12 field trials used winter wheat. For the spring wheat tests, pyraflufen-ethyl (25 g a.i./L emulsifiable concentrate, EC, formulation) was applied as a combination of a preplant soil broadcast application and a postemergence broadcast foliar application, each at 1.8 g a.i./ha, with a 28-49-day retreatment interval, for a total of 3.6 g a.i./ha/season. For the winter wheat tests, pyraflufen-ethyl (25 g a.i./L, EC) was applied as a single postemergence broadcast foliar application at 1.8 g a.i./ha. All applications were made in 56-117 L/ha spray volumes using ground equipment and included a crop-oil concentrate (COC) at 0.5% of the spray volume. Wheat forage samples were harvested 6-7 days after the last application (DALA) when the wheat was at 6-8 inch height to stem elongation growth stage. Hay samples were cut at early flowering (boot stage) to soft dough stage (21-85 DALA) and allowed to field-dry for 1-8 days prior to collection. Grain and straw samples were harvested at normal maturity, 56-113 DALA. Data from the two residue decline tests indicated that residues of both pyraflufen-ethyl and E-1 declined in wheat forage at longer post-treatment intervals. As residues of both analytes were not detected in/on any hay, grain and straw samples, no pattern of decline could be determined for these commodities.

Commodity	Total Application Rate/ Method (g a.i./ha)	PHI (days)	Residue Levels (ppm)							
			n	Min[#]	Max[#]	LAFT[*]	HAFT[*]	Median[*]	Mean[*]	SD[*]
Combined residues of pyraflufen-ethyl and metabolite E-1										
Wheat forage	9.7-10.1 g a.i./ha (preplant; SC)	28-153	3	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A
Wheat hay		50-212	3	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A
Wheat grain		96-225	3	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A
Wheat straw		96-225	3	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A
Wheat forage	10.1 g a.i./ha (preplant; EC)	153	1	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A
Wheat hay		212	1	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A
Wheat grain		225	1	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A
Wheat straw		225	1	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A
Wheat forage	1.8 g a.i./ha (preplant) + 1.8 g a.i./ha (postemergence)	7	8	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A
Wheat hay		21-33	8	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A
Wheat grain		56-69	8	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A
Wheat straw		56-69	8	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A
Wheat forage	1.8 g a.i./ha (postemergence)	6-7	12	<0.01	<0.017	<0.01	<0.016	0.01	0.011	0.002
Wheat hay		26-85	12	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A
Wheat grain		76-113	12	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A
Wheat straw		76-113	12	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	N/A

[#] Values based on total number of samples.

[*] Values based on per-trial averages. LAFT = Lowest Average Field Trial. HAFT = Highest Average Field Trial, SD = Standard Deviation. For computation of the LAFT, HAFT, median, mean and standard deviation, values <LOQ are assumed to be at the LOQ.

n = number of field trials.

PROCESSED FOOD AND FEED – Spring wheat	**PMRA# 2130301**
Test Site	One trial in NAFTA Growing Region 7 (NE)
Treatment	Preplant (9.1 g a.i./ha) + postemergence broadcast foliar application (9.1 g a.i./ha)
Total Rate	18.2 g a.i./ha
End-use product/formulation	25 g/L emulsifiable concentrate (EC) formulation
Preharvest interval	56 days
Processed Commodity	**Average Processing Factor**

Pyraflufen-ethyl residues were all <LOQ (<0.01 ppm) in wheat grain, bran, flour, middlings, shorts and germ. Processing factors could not be calculated for pyraflufen-ethyl in wheat processed fractions.

PROCESSED FOOD AND FEED - Soybean	**PMRA# 2130304**
Test Site	One trial in NAFTA Growing Region 5 (IL)
Treatment	Preplant (9.2 g a.i./ha) + postemergence broadcast foliar application (9.0 g a.i./ha)
Total Rate	18.2 g a.i./ha
End-use product/formulation	Emulsifiable concentrate (EC) formulation, 25 g/L
Preharvest interval	84 days
Processed Commodity	**Average Processing Factor**

Pyraflufen-ethyl residues were all <LOQ (<0.01 ppm) in soybean seed, meal, hulls and refined oil. Processing factors could not be calculated for pyraflufen-ethyl in soybean processed fractions.

PROCESSED FOOD AND FEED – Field corn	**PMRA# 2130303**
Test Site	One trial in NAFTA Growing Region 5 (NE)
Treatment	Preplant (9.2 g a.i./ha) + postemergence broadcast foliar application (9.1 g a.i./ha)
Total Rate	18.3 g a.i./ha
End-use product/formulation	Emulsifiable concentrate (EC) formulation, 25 g/L
Preharvest interval	103 days
Processed Commodity	**Average Processing Factor**

Pyraflufen-ethyl residues were <LOQ (<0.01 ppm) in field corn grain, grits, meal, flour, refined oil and starch. Processing factors could not be calculated for pyraflufen-ethyl in field corn processed fractions.

LIVESTOCK FEEDING – Dairy cattle	**PMRA# 2130309**

Lactating dairy cows were administered pyraflufen-ethyl at dose levels of 1.0, 3.1 and 9.8 ppm in the feed for 29 consecutive days. The dose levels correspond to 25x, 78x and 245x, respectively, of the estimated more balanced diet (MBD) for dairy cattle, and 100x, 310x and 980x of the MBD for beef cattle.

Commodity	**Feeding Level (ppm)**	**Residues (ppm)**		**MBD (ppm)**	**Anticipated Combined Residues at MBD (ppm)**
		PFE	**E-1**		
Milk	1.0	<0.01-0.0107	<0.01	0.01 (beef cattle); 0.04 (dairy cattle)	<0.001
	3.1	<0.01	<0.01		<0.001
	9.8	<0.01	<0.01-0.010		<0.001
Kidney	1.0	<0.01	<0.01		<0.001
	3.1	<0.01	<0.01-0.012		<0.001
	9.8	<0.01	0.019-0.045		<0.001
Muscle	1.0 / 3.1 / 9.8	<0.01	<0.01		<0.001
Liver	1.0 / 3.1 / 9.8	<0.01	<0.01		<0.001
Fat	1.0 / 3.1 / 9.8	<0.01	<0.01		<0.001

Table 6 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES			
RESIDUE DEFINITION FOR ENFORCEMENT **Primary and Rotational crops**		Pyraflufen-ethyl and Metabolite E-1	
RESIDUE DEFINITION FOR RISK ASSESSMENT **Primary and Rotational crops**		Pyraflufen-ethyl and Metabolite E-1	
METABOLIC PROFILE IN DIVERSE CROPS		Similar in wheat, cotton and potato	
ANIMAL STUDIES			
ANIMALS		**Ruminant and Poultry**	
RESIDUE DEFINITION FOR ENFORCEMENT		Pyraflufen-ethyl and Metabolite E-1	
RESIDUE DEFINITION FOR RISK ASSESSMENT		Pyraflufen-ethyl and Metabolite E-1	
METABOLIC PROFILE IN ANIMALS		Similar in goat, hen, rat	
FAT SOLUBLE RESIDUE		No	
DIETARY RISK FROM FOOD AND WATER			
Basic chronic non-cancer dietary exposure analysis **ADI = 0.2 mg/kg bw/day** **Estimated chronic drinking water concentration = 0.34 μg/L**	**POPULATION**	**ESTIMATED RISK** **% of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food Alone	**Food and Water**
	All infants <1 year	<1.0	<1.0
	Children 1–2 years	<1.0	<1.0
	Children 3–5 years	<1.0	<1.0
	Children 6–12 years	<1.0	<1.0
	Youth 13–19 years	<1.0	<1.0
	Adults 20–49 years	<1.0	<1.0
	Adults 50+ years	<1.0	<1.0
	Females 13–49 years	<1.0	<1.0
	Total population	<1.0	<1.0
Intermediate cancer dietary exposure analysis $q_1^* = 0.0157\ (\text{mg/kg bw/day})^{-1}$ **Estimated chronic drinking water concentration = 0.34 μg/L**	**POPULATION**	**ESTIMATED LIFETIME CANCER RISK**	
		Food Alone	**Food and Water**
	Total population	1.3×10^{-6}	1.5×10^{-6}

Table 7 Major groundwater and surface water model inputs for Level 1 assessment of pyraflufen-ethyl and its major transformation products E-1, E-2, E-3 and E-9

Type of Input	Parameter	Value
Application Information	Crop(s) to be treated	Spring wheat, field corn and soybeans
	Maximum allowable application rate per year (g a.i./ha)	4.5
	Maximum rate each application (g a.i./ha)	4.5
	Maximum number of applications per year	1
	Minimum interval between applications (days)	N/A

Type of Input	Parameter	Value
	Method of application	Ground foliar to weeds only, no direct contact to crops
Environmental Fate Characteristics	Hydrolysis half-life at pH 7 (days)	Stable for the combined residue modelling
	Photolysis half-life in water (days)	5 for the combined residue
	Adsorption K_d (mL/g)	2.27 (20th percentile of three K_d values of E-1) for the combined residue modelling
	Aerobic soil biotransformation half-life (days)	673 (90th percentile confidence bound on mean of six half-life values adjusted to 25°C) for the combined residue modelling
	Aerobic aquatic biotransformation half-life (days)	436 (longest of two half-lives) for the combined residue modelling
	Anaerobic aquatic biotransformation half-life (days)	2088 (the only half-life available) for the combined residue modelling

Table 8 Fate and behaviour in the terrestrial environment.

Property	Value	Major Transformation products	Comments	PMRA#
Abiotic transformation				
Hydrolysis	DT_{50}: -pH4 = stable -pH7 = 10.8d -pH 9 < 2.4hr	E-1; stable to further hydrolysis at all pHs.	Hydrolyses at neutral pH and shows a high potential to hydrolyze at higher pH.	2130063 2268941
Phototransformation in soil	DT_{50} = 2 d	E-1 E-2	Undergoes phototransformation in soil. Transformation is faster in the dark.	2268953
Biotransformation				
Biotransformation in aerobic soil	DT_{50} Active: < 1d Total Residues*: 326-1630 d (80th% = 557d)	E-1 E-2 E-3	Soil biotransformation is very rapid. Mean half-life for E-1 was 14d. E-2 and E-3 are persistent and may accumulate in soil. Total residues* are persistent in soils and may carry over to the next season.	2268973 2268966 2268961 2130168 2268982 2268985
Biotransformation in anaerobic soil	DT_{50} = 1d	E-1 (99%, DT_{50}= 191d) E-2 (28%, DT_{50}= 392d)	Rapid degradation in flooded soil. Major transformation products are persistent.	2130171 2130172
Mobility				
Adsorption / desorption in soil	Active Koc = 2000 E-1 Koc = 81-197 E-2 Koc = 1424-2179 E-3 Koc = 3098-4354	-	Mobility: Active: slight E-1: high E-2: low E-3: slight	2268992 2269055 2269058 2269070

Soil leaching	-	-	The active and its major products do not leach below 15cm depth. leachate: 0.2-0.5%	2269053 2269069
Volatilization	NA	-	Not volatile	-
Field studies				
Field dissipation/ Field leaching	DT_{50}<1d	E-1 (DT_{50}= 10.5-161d), E-2 E-3	Parent dissipates within hours. Residues were not found in soil layers below 15cm depth.	2130238 2269066
*Total residues is the sum of the parent, E-1, E-2, E-3 and E-9 products, as appropriate.				

Table 9 Fate and behaviour in the aquatic environment

Study type	Value	Major Transformation products	Comments	PMRA#
Abiotic transformation				
Hydrolysis	DT_{50}: pH4 = stable pH7 = 10.8d pH 9 < 2.4h	E-1 (stable to further hydrolysis at all pHs).	Hydrolyses at neutral pH and shows a high potential to hydrolyze at higher pH.	2130063, 2268941
Phototransformation in water	DT_{50}= 5d (12 h cycle)	Possibly PD-1 (one label only)	Active photolyzes in water.	2269071, 2269075
Biotransformation				
Biotransformation in aerobic water systems	Active: DT_{50}/ $DT_{90water}$= <6 h DT_{50}/ $DT_{90system}$= <6 h Total Residues*: $DT_{50system}$= 274-436d	E-1 E-2	Rapid degradation occurs in water/sediment systems. E-1 mainly found in water but also in sediment, E-2 is persistent, only found in sediment. Total residues* are persistent in the system.	2268990
Biotransformation in anaerobic water systems	Active: DT_{50}/ $DT_{90water}$= <4 h DT_{50}/ $DT_{90system}$= <4 h Total Residues*: $DT_{50system}$= 2088d	E-1 E-2	Rapid degradation of active occurs in water/sediment systems. E-2 is persistent and accumulates in the sediment. Total residues are persistent in the system.	2268987
Partitioning				
Adsorption / desorption in sediment	-	-	Major products : E-1 can partition to sediment to some extent, mostly found in water, E-2 is only found in sediment. Minor product E-3 accumulates in sediment.	2268990 2268987
Bioconcentration	18X	-	The major transformation product E-1 has a low potential for bioconcentration	2269067
Field studies				
Field dissipation	NA			

*Total residues is the sum of the parent, E-1, E-2, E-3 and E-9 products, as sppropriate. NA: Not available.

Table 10 EECs in soil and water*

Compartment		TGAI		E-1 (transformation product)	
		EEC	Drift (6%) EEC		
Soil		0.002 mg /kg	1.2E-4 mg /kg	-	-
Water	80cm	0.56 µg/L	0.034 µg/L	0.52ug/L	0.03 µg/L
	15cm	3 µg/L	0.18 µg/L	2.8 µg/L	0.17 µg/L
Runoff	80cm	Peak: 0.43 µg/L 21d: 0.41 µg/L	-	Peak: 0.4 µg/L 21d: 0.41 µg/L	-
	15cm	Peak: 1.7 µg/L 21d: 1.2 µg/L	-	Peak: 1.6 µg/L 21d: 1.1 µg/L	-

*Application of pyraflufen-ethyl at 1 X 4.5g a.i./ha.

Table 11 Level 1 aquatic ecoscenario modelling EECs (µg a.i./L) for pyraflufen-ethyl combined residue in a water body 0.8 m deep, excluding spray drift

Region-crop	EEC (µg a.i./L)					
	Peak	96-h	21-day	60-day	90-day	Yearly
BC-wheat	0.093	0.091	0.087	0.087	0.087	0.067
BC-corn	0.010	0.010	0.009	0.008	0.007	0.004
Prairie-wheat	0.11	0.10	0.10	0.093	0.089	0.070
Prairie-corn and soybeans	0.21	0.21	0.19	0.18	0.17	0.14
ON-corn and soybeans	0.21	0.21	0.20	0.18	0.17	0.11
QC-corn and soybeans	0.24	0.23	0.22	0.21	0.20	0.15
Atlantic-wheat, corn and soybeans	0.43	0.43	0.41	0.38	0.35	0.24
Max	0.43	0.43	0.41	0.38	0.35	0.24

Table 12 Level 1 aquatic ecoscenario modelling EECs (µg a.i./L) for pyraflufen-ethyl combined residue in a water body 0.15 m deep, excluding spray drift

Region-crop	EEC (µg a.i./L)					
	Peak	96-h	21-day	60-day	90-day	Yearly
BC-wheat	0.34	0.31	0.24	0.17	0.15	0.068
BC-corn	0.041	0.037	0.026	0.017	0.014	0.005
Prairie-wheat	0.39	0.35	0.26	0.19	0.17	0.081
Prairie-corn and soybeans	0.74	0.68	0.50	0.35	0.30	0.15
ON-corn and soybeans	0.75	0.67	0.56	0.41	0.35	0.15
QC-corn and soybeans	0.85	0.80	0.62	0.42	0.35	0.15
Atlantic-wheat, corn and soybeans	1.7	1.6	1.2	0.83	0.70	0.30
Max	1.7	1.6	1.2	0.83	0.70	0.30

Table 13 Toxicity of pyraflufen-ethyl and its end-use product to terrestrial organisms

Organism	Test substance	Exposure	Toxicity Endpoint	Degree of toxicity[a]	Corrected Toxicity Endpoint [b]	PMRA#
Invertebrates						
Earthworm	TGAI	14d-Acute	LC_{50} >1000 mg/kg	-	LC_{50} >500 mg/kg	2130067 2130181
	TGAI	2 month	NOEC > 500 mg a.i./kg	-	NOEC > 500 mg a.i./kg	2130184
Bee	TGAI	48h-Oral	LC_{50} >112 µg a.i./bee	RNT[4]	LC_{50} >112 µg a.i./bee	2269553
		48h-Contact	LC_{50} >100 µg a.i./bee	RNT	LC_{50} >100 µg a.i./bee	2130182
	EP	96h-Oral	LD_{50} < 4.27 µg a.i./bee	MT[3]	LD_{50} < 4.27 µg a.i./bee	2130313
		96h-Contact	LD_{50} = 9.82 µg a.i./bee (392.8 µg EP/bee)	RNT[5]	LD_{50} = 9.82 µg a.i./bee (392.8 µg EP/bee)	
Predatory arthropod, mite	EP	7d-Contact	LR_{50} < 1.6L/ha NOEC < 1.6L/ha	-	LR_{50} < 1.6L/ha NOEC < 1.6L/ha	2222195
Parasitic arthropod, wasp	EP	24h-Contact	LR_{50} < 1.6L/ha NOEC < 1.6L/ha	-	LR_{50} < 1.6L/ha NOEC < 1.6L/ha	2222197
Birds						
Bobwhite quail	TGAI	15d-Acute	LD_{50}> 2000 mg/kg bw	PNT[2]	LD_{50}> 200 mg/kg bw	2269565
	TGAI	8d-Dietary	LC_{50}: >5000 ppm (>1085 mg/kg bw) NOEC: 5000 ppm (1085 mg/kg bw)	PNT	LC_{50}: >500 ppm (>108.5 mg/kg bw) NOEC: 500 ppm (108.5 mg/kg bw)	2269560
	TGAI	Reproduction	NOAEC: 4836 mg/kg dw; LOAEC: >4836 mg/kg dw (513.4 mg/kg bw)	-	NOAEC: 4836 mg/kg dw; LOAEC: >4836 mg/kg dw (513.4 mg/kg bw)	2269514
Mallard duck	TGAI	Acute	-	-	-	-
		8d-Dietary	LC_{50}: >5000 ppm (> 1572 mg/kg bw) NOEC: 5000 ppm (1572 mg/kg bw)	PNT	LC_{50}: >500 ppm (> 157.2 mg/kg bw) NOEC: 500 ppm (157.2 mg/kg bw)	2269564
		Reproduction	NOAEC: 324 mg/kg dw (18.3 mg/kg bw) LOAEC: 3240 mg/kg dw	-	NOAEC: 324 mg/kg dw (18.3 mg/kg bw) LOAEC: 3240 mg/kg dw	2269533
Mammals						
Rat	TGAI	96h Acute	LD_{50} >5000 mg/kg bw	PNT	LD_{50} >500 mg/kg bw	2130100
	EP	96h Acute	LD_{50} = 3712 mg/kg bw (females)	PNT	LD_{50} = 371.2 mg/kg bw (females)	2130268
	TGAI	Reproduction	NOAEL = 1000 ppm diet; (70.8 mg/kg bw (males)) Pup wt.	-	NOAEL = 1000 ppm diet; (70.8 mg/kg bw (males)) Pup wt.	2130123 2130124
Mouse	TGAI	96h Acute	LD_{50} >5000 mg/kg bw	PNT	-	2130099
Vascular plants						
Terrestrial Vascular plants	EP	14d-Seedling emergence	EC_{25} = 1.3 g a.i./ha	-	EC_{25} = 1.3 g a.i./ha	2269535 2130205
	EP	24d-Vegetative vigour	HD_5 = 0.19 g a.i./ha (SSD based on EC_{50}[1])	-	HD_5 = 0.19 g a.i./ha (SSD based on EC_{50}[1])	2269536 2130204
	EP	14d-Vegetative vigour	EC_{25} = 2.69 g a.i./ha	-	EC_{25} = 2.69 g a.i./ha	2269519 2130203

[a] Atkins et al.(1981) for bees and USEPA classification for others, where applicable. [b] Corrected endpoint is used in the risk assessment, see Table 7.3 for uncertainty factors applied; [1] SSD is based on EC_{50} for cucumber lettuce, turnip, tomato, onion, and soybean, 0.55, 0.33, 0.46, 0.45, 2.1, 1.2 g a.i./ha, respectively.[2] PNT: Practically non-toxic; [3]MT: Moderately toxic; [4] RNT: Relatively non-toxic; [5] The EP is contributing to toxicity, thus this endpoint is considered RNT.

Table 14 Toxicity of pyraflufen-ethyl, its end-use product and the major transformation product E-1 to aquatic organisms

Organism	Test substance	Exposure	Toxicity Endpoint	Degree of toxicity[a]	Corrected Toxicity Endpoint [b]	PMRA#
Freshwater species						
Invertebrates						
Water flea, *Daphnia* sp.	TGAI	48h-Acute	EC_{50} >82 µg a.i./L	VHT*[4]	EC_{50} >41 µg a.i./L	2269568
	TGAI	21d-Chronic	NOEC = 81 µg a.i./L reproduction	-	NOEC = 81 µg a.i./L reproduction	2269578
	EP[1]	48h-Acute	EC_{50} = 20 µg a.i./L (760 µg EP/L)	VHT	EC_{50} = 10 µg a.i./L (380 µg EP/L)	2269521
	E-1[2]	48h-Acute	EC_{50} > 121 mg/L	PNT[3]	EC_{50} > 60.5 mg/L	2269608
	E-1	21d-Chronic	NOEC = 99mg/L (# offspring)	-	NOEC = 99mg/L (# offspring)	2269538
Midge, *Chironomus* sp.	TGAI	21d-Chronic	NOEC ≥ 54 µg a.i./L, emergence	-	NOEC ≥ 54 µg a.i./L, emergence	2269622
Fish/amphibians						
Rainbow trout *Onchorhincus* sp.	TGAI	96h-Acute	LC_{50} > 101 µg a.i./L	VHT*	LC_{50} > 10.1 µg a.i./L	2269583
	EP (2% SC)	96h-Acute	LC_{50} > 2520 µg a.i./L (>126 mg EP/L)	PNT	LC_{50} > 252 µg a.i./L (>12.6 mg EP/L)	2269619
	E-1	96h-Acute	LC_{50} > 118 mg/L	PNT	LC_{50} > 11.8 mg/L	2269537
Bluegill sunfish *Lepomis* sp.	TGAI	96h-Acute	LC_{50} > 85 µg a.i./L	VHT*	LC_{50} > 8.5 µg a.i./L	2130191
	EP	96h-Acute	EC_{50} = 86 µg a.i./L (3.3 mg EP/L)	VHT	EC_{50} = 8.6 µg a.i./L (0.33 mg EP/L)	2269526
	E-1	96h-Acute	EC_{50} > 90 mg/L	ST[5]	EC_{50} > 9.0 mg/L	2269525
Fathead minnow *Pimephales* sp.	TGAI	28d ELS	NOEC: 3.4 µg a.i./L, growth	-	NOEC: 3.4 µg a.i./L, growth	2269576
	TGAI	28d ELS (High UV)	NOEC: 0.89 µg a.i./L, growth	-	NOEC: 0.89 µg a.i./L, growth	2269637 2269639
	E-1	28d ELS	LC_{50}>10 mg/L NOEC: 10 mg/L	-	LC_{50}>1.0 mg/L NOEC: 10 mg/L	2269550
Amphibians[c]	EP	96h-Acute	EC_{50} = 86 µg a.i./L (3.3 mg EP/L)	VHT	EC_{50} = 8.6 µg a.i./L (0.33 mg EP/L)	2269526
	TGAI	28d ELS (High UV)	NOEC: 0.89 µg a.i./L, growth	-	NOEC: 0.89 µg a.i./L, growth	2269637 2269639
	E-1	28d ELS	LC_{50}>10 mg/L NOEC: 10 mg/L	-	LC_{50}>1.0 mg/L NOEC: 10 mg/L	2269550
Freshwater alga						
Green alga, *Anabaena* sp.	EP	96h-Acute	EC_{50} = 34 µg a.i./L	-	EC_{50} = 17 µg a.i./L	2269592 2222199
Green alga *Pseudokirch./ Selenastrum* sp.[d]	EP	96h-Acute	EC_{50} = 2.6 µg a.i./L	-	EC_{50} = 1.3 µg a.i./L	2269598 2222200
	TGAI	72h-Acute	EC_{50} = 0.31 µg a.i./L	-	EC_{50} = 0.16 µg a.i./L	2130201
	E-1	72h-Acute	EC_{50} = 2.2 µg /L	-	EC_{50} = 1.1 µg /L	2130202
Diatom *Navicula* sp.	EP	96h-Acute	EC_{50} = 1.5 µg a.i./L	-	EC_{50} = 0.75 µg a.i./L	2269602
	TGAI	72h-Acute	EC_{50} = 1.6 µg a.i./L	-	EC_{50} = 0.76 µg a.i./L	2130197
	E-1	72h-Acute	EC_{50} = 1700 µg/L	-	EC_{50} = 850 µg/L	2130198
Vascular plant						
Duck weed *Lemna* sp.	EP	7d	EC_{50} = 16 µg a.i./L	-	EC_{50} = 8 µg a.i./L	2269595 2222203
	E-1	7d	EC_{50} = 2.6 µg /L	-	EC_{50} = 1.3 µg /L	2130206
Marine species						
Invertebrates						
Eastern Oyster	E-1	96h-Acute	EC_{50} > 67,000 µg/L	ST	EC_{50} > 33,500 µg/L	2269539
	TGAI	96h-Acute	EC_{50} > 43 µg a.i./L	VHT*	EC_{50} > 21.5 µg a.i./L	2269610

Mysid shrimp	E-1	96h-Acute	LC$_{50}$ = 9.4 mg/L	MT[6]	LC$_{50}$ = 4.7 mg/L	2269549
Fish						
Sheepshead minnow	TGAI	96h-Acute	LC$_{50}$ > 56 μg a.i./L	VHT[*]	LC$_{50}$ > 5.6 μg a.i./L	2269566
	E-1	96h-Acute	LC$_{50}$ > 99 mg /L	PNT	LC$_{50}$ > 9.9 mg /L	2269544
Algae						
Diatom *Skeletonema* sp.	EP	96h-Acute	LC$_{50}$ = 10 μg a.i./L	-	LC$_{50}$ = 5 μg a.i./L	2269601 2222201

[a] USEPA classification, where applicable. [b] Corrected endpoint is used in the risk assessment, see Table 7.3 for uncertainty factors applied; NOEC values are not corrected; [c] Based on fish ELS study; [d] *Pseudokirchnieriella* sp. Is the same as *Selenastrum* sp. ie. formerly known as *Selenastrum* sp. [1] EP: End-use product ET-751 2.5% EC, [2] E-1 = major transformation product; [3] PNT: Practically non-toxic; [4] VHT: Very highly toxic; [5] ST: Slightly toxic; [6] MT: Moderately toxic; [*] This endpoint is a "greater than" value limited to the maximum solubility of the active and does not represent true toxic effects

Table 15 Endpoints used in the risk assessment

Organism	Test substance	Exposure	Toxicity Endpoint	Corrected Toxicity Endpoint[1]	Uncertainty factor applied[2]
Terrestrial organisms					
Earthworm	TGAI[3]	14d-Acute	LC$_{50}$ >1000 mg/kg	LC$_{50}$ >500 mg/kg	2
Bee	TGAI	48 h-Oral	LC$_{50}$ >112 μg a.i./bee	LC$_{50}$ >112 μg a.i./bee	1
Bee	EP[4]	96h-Contact	LD$_{50}$ = 9.82 μg a.i./bee (392.8 μg EP/bee)	LD$_{50}$ = 9.82 μg a.i./bee (392.8 μg EP/bee)	1
Beneficial Insects (Parasitic wasp)	EP	7d-Contact	LR$_{50}$ < 1.6L/ha NOEC < 1.6L/ha	LR$_{50}$ < 1.6L/ha NOEC < 1.6L/ha	1
Birds (Bobwhite quail/Mallard duck)	TGAI	15d-Acute	LD$_{50}$> 2000 mg/kg bw	LD$_{50}$> 200 mg/kg bw	10
		8d-Dietary	LC$_{50}$: >5000 ppm (>1085 mg/kg bw) NOEC: 5000 ppm (1085 mg/kg bw)	LC$_{50}$: >500 ppm (>108.5 mg/kg bw) NOEC: 500 ppm (108.5 mg/kg bw)	10
		Reproduction	NOAEC: 4836 mg/kg dw; LOAEC: >4836 mg/kg dw (513.4 mg/kg bw)	NOAEC: 4836 mg/kg dw; LOAEC: >4836 mg/kg dw (513.4 mg/kg bw)	1
Mammals (Rat)	EP	96h Acute	LD$_{50}$ = 3712 mg/kg bw (females)	LD$_{50}$ = 371.2 mg/kg bw (females)	10
	TGAI	Reproduction	NOAEL = 1000 ppm diet; (70.8 mg/kg bw (males)) Pup wt.	NOAEL = 1000 ppm diet; (70.8 mg/kg bw (males)) Pup wt.	1
Terrestrial vascular plants	EP	Vegetative vigour	HD$_5$ = 0.19 g a.i./ha (SSD based on EC$_{50}$)	HD$_5$ = 0.19 g a.i./ha (SSD based on EC$_{50}$)	1
Aquatic organisms					
Freshwater invertebrates (*Daphnia* sp)	EP	48h-Acute	EC$_{50}$ = 20 μg a.i./L (760 μg EP/L)	EC$_{50}$ = 10 μg a.i./L (380 μg EP/L)	2
	TGAI	21d-Chronic	NOEC = 81 μg a.i./L reproduction	NOEC = 81 μg a.i./L reproduction	1
Midge, *Chironomus* sp.	TGAI	21d-Chronic	NOEC ≥ 54 μg a.i./L, emergence	NOEC ≥ 54 μg a.i./L, emergence	1
Freshwater fish (Bluegill sunfish)	EP	96h-Acute	EC$_{50}$ = 86 μg a.i./L (3.3 mg EP/L)	EC$_{50}$ = 8.6 μg a.i./L (0.33 mg EP/L)	10
Freshwater fish (Fathead minnow)	TGAI	28d ELS	NOEC: 3.4 μg a.i./L, growth NOEC: 0.89 μg a.i./L, growth (High UV light)	NOEC: 3.4 μg a.i./L, growth NOEC: 0.89 μg a.i./L, growth (High UV light)	1
Freshwater fish (Fathead minnow)	E-1	28d ELS	NOEC: 10 mg/L	NOEC: 10 mg/L	1
Amphibians (based on fish acute EC$_{50}$ and ELS NOEC)	EP	96h-Acute	EC$_{50}$ = 86 μg a.i./L (3.3 mg EP/L)	EC$_{50}$ = 8.6 μg a.i./L (0.33 mg EP/L)	10
	TGAI	28d ELS	NOEC: 0.89 μg a.i./L, growth (High UV light)	NOEC: 0.89 μg a.i./L, growth (High UV light)	1
	E-1	28d ELS	NOEC: 10 mg/L	NOEC: 10 mg/L	1
Aquatic vascular	E-1	7d	EC$_{50}$ = 2.6 μg a.i./L	EC$_{50}$ = 1.3 μg a.i./L	2

plants (*Lemna*)					
Algae (*Selenastrum*)	TGAI	72h-Acute	EC_{50} = 0.31 µg a.i./L	EC_{50} = 0.16 µg a.i./L	2
	E-1	72h-Acute	EC_{50} = 2.2 µg /L	EC_{50} = 1.1 µg /L	
Saltwater invertebrates (oyster)	TGAI	96h-Acute	EC_{50} > 43 µg a.i./L	EC_{50} > 21.5 µg a.i./L	2
Saltwater fish (sheepshead minnow)	TGAI	96h-Acute	LC_{50} > 56ug a.i./L	LC_{50} > 5.6 µg a.i./L	10
Saltwater algae (*Skeletonema*)	EP	96h-Acute	EC_{50} = 10 µg a.i./L	EC_{50} = 5 µg a.i./L	2

[1] Corrected values are derived using the uncertainty factors in this table; [2] According to EAD guidance; [3] TGAI: technical grade active ingredient; [4]EP: end-use product;

Table 16 Risk to terrestrial invertebrates and plants

Organism	**Exposure**	**Test Substance**	**Endpoint value**	**EEC[2]**	**RQ[3]**	**Risk LOC[4] Exceeded**
Screening Level Risk Assessment: Overspray						
Invertebrates						
Earthworm	Acute	TGAI	LC_{50} >500 mg/kg	0.002 mg a.i./kg	<<1	NO
Bee[5]	Oral	TGAI	LC_{50} >112 µg a.i./bee	0.13 µg a.i./bee	<0.1	NO
	Contact	EP	LC_{50} = 9.82 µg a.i./bee 392.8 µg EP/bee	0.01 µg a.i./bee 0.43 µg EP/bee	<0.1	NO
	Brood / hive	NA	NA	NA	NA	NA
Predatory arthropod	Contact	EP	LR_{50} < 1.6L/ha	0.18L/ha	>0.11	NA
Parasitic arthropod	Contact	EP	LR_{50} < 1.6L/ha	0.18L/ha	>0.11	NA
Vascular plants						
Vascular plants	Vegetative vigour	EP	HD_5 = 0.19 g a.i./ha (SSD based on EC_{50})	4.5 g a.i./ha	**23.7**	**YES**
	14d-Seedling emergence	EP	EC_{25} = 1.3 g a.i./ha	4.5 g a.i./ha	**3.46**	**YES**
Refined Risk Assessment: Spray Drift						
Vascular plants	Vegetative vigour	EP	HD_5 = 0.19 g a.i./ha	6% Drift[1]		
				0.27 g a.i./ha	**1.42**	**YES**
	14d-Seedling emergence	EP	EC_{25} = 1.3 g a.i./ha	0.27 g a.i./ha	0.2	NO

[1] Drift at 1m distance from site of application is 6% of applied rate using a ground boom and medium droplet size.

[2]Estimated Environmental Concentration (EEC),

[3]Risk Quotient (RQ) = exposure/toxicity;

[4]Level of Concern (LOC), bolded cells indicate that the RQ exceeds the LOC, triggering a refined risk assessment using drift; NA: Not available/applicable;

[5] EECs for bees: TGAI: Contact exposure EEC= (2.4 µg a.i./bee per kg/ha) × (0.0045 kg a.i./ha) = 0.01 µg a.i./bee; EP: Contact exposure EEC= (2.4 µg EP/bee per kg/ha) × (0.18 kg EP/ha) = 0.43 µg EP/bee; TGAI: Oral exposure EEC= (29 µg a.i./bee per kg/ha) × (0.0045 kg a.i./h) = 0.13 µg a.i./bee. The oral exposure estimate for adult bees is calculated by multiplying the direct single rate by 29 µg a.i./bee per kg/ha. This conversion is based on consumption rates primarily derived from Rortais et al. (2005) and Crailsheim et al. (1992 and 1993). For the contact exposure estimate for bees, a conversion from kg a.i./ha to µg a.i./bee was required. The proposed upper-bound residue value for estimating exposure to bees is based on the maximum residue value reported by Koch and Weißer (1997); 2.4 µg a.i./bee per kg/ha.

Table 17 Risk to Birds and Mammals (Screening Assessment)

Birds					
Size	**Food type**	**Endpoint**	**Toxicity[1] (mg a.i./kg bw/d)**	**EDE[3] (mg a.i./kg bw)**	**RQ[2]**
Small	Small insects	Acute	200	0.226	<0.1
		Reproduction	18.3	0.226	<0.1
Medium	Small insects	Acute	200	0.177	<0.1
		Reproduction	18.3	0.177	<0.1
Large	Short grass	Acute	200	0.185	<0.1
		Reproduction	18.3	0.185	<0.1

Mammals					
Size	**Food type**	**Endpoint**	**Toxicity (mg a.i./kg bw/d)**	**EDE (mg a.i./kg bw)**	**RQ**
Small	Small insects	Acute	371	0.129	<0.1
		Reproduction	70.8	0.129	<0.1
Medium	Short grass	Acute	371	0.397	<0.1
		Reproduction	70.8	0.397	<0.1
Large	Short grass	Acute	371	0.218	<0.1
		Reproduction	70.8	0.218	<0.1

[1] Endpoints were divided by an uncertainty factor to account for varying protection goals (in other words, protection at the community, population, or individual level)

[2] RQ = exposure/toxicity; RQs < 0.1 were not calculated to show all decimal points. RQs are based on estimated environmental concentrations (EEC): For birds and mammals, the EEC takes into account the maximum seasonal cumulative rate on vegetation and is calculated using PMRA standard methods based on the Hoerger and Kenaga nomogram as modified by Fletcher (1994)

[3] EDE = Estimated dietary exposure; calculated for each bird or mammal size based on the EEC on appropriate food item for each food guild (at the screening level, the most conservative EEC for each food guild was used). The EDE was calculated using the following formula: (FIR/BW) × EEC. For each body weight (BW), the food ingestion rate (FIR) was based on equations from Nagy (1987). For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used; for mammals, the "all mammals" equation was used:

Passerine Equation (body weight ≤200 g): FIR (g dry weight/day) = 0.398(BW in g) $^{0.850}$

All Birds Equation (body weight > 200 g): FIR (g dry weight/day) = 0.648(BW in g) $^{0.651}$

All Mammals Equation: FIR (g dry weight/day) = 0.235(BW in g) 0.822

Conversion from a concentration (EEC) to a dose (EDE): [EDE (mg a.i./kg bw) = EEC (mg a.i./kg diet)/BW (g) × FIR (g diet/day)] Nagy, K.A. 1987. Field metabolic rate and food requirement scaling in mammals and birds. Ecological Monographs 57:111-128

Table 18 Risk to aquatic organisms

Organism	Test substance	Exposure	Corrected Toxicity Endpoint[2]	EEC	RQ	LOC Exceeded?
Screening Assessment (overspray)						
Freshwater species						
Freshwater invertebrates (*Daphnia* sp.)	EP[3]	48h-Acute	EC_{50} = 10 µg a.i./L (380 µg EP/L)	0.56 µg a.i./L (E-1: 0.52 µg/L)	<0.1	NO
	TGAI[4]	21d-Chronic	NOEC = 81 µg a.i./L, reproduction		<0.1	
Midge, *Chironomus* sp.	TGAI	21d-Chronic	NOEC ≥ 54 µg a.i./L, emergence		<0.1	
Freshwater fish (Bluegill sunfish)	EP	96h-Acute	EC_{50} = 8.6 µg a.i./L (0.33 mg EP/L)		<0.1	
Freshwater fish (fathead minnow)	TGAI	28d ELS (High UV)	NOEC: 0.89 µg a.i./L, growth		0.63	
	E-1	28d ELS	NOEC: 10 mg/L		<0.1	
Amphibians (based on fish acute and ELS	EP	96h-Acute	EC_{50} = 8.6 µg a.i./L (0.33 mg EP/L)	3.0 µg a.i./L (E-1: 2.8 µg/L)	0.34	
	TGAI	28d ELS	NOEC: 3.4 µg a.i./L,		0.88	

study)			growth			
			NOEC: 0.89 µg a.i./L, growth (High UV light)		**3.4**	**YES**
	E-1	28d ELS	NOEC: 10 mg/L		<0.1	NO
Aquatic vascular plants (*Lemna*)	E-1	7d	EC_{50} = 1.3 µg a.i./L	0.56 µg a.i./L (E-1: 0.52 µg/L)	0.4	NO
Algae (*Selenastrum*)	TGAI	72h-Acute	EC_{50} = 0.16 µg a.i./L		**3.5**	**YES**
Marine species						
Saltwater invertebrates (oyster)	TGAI	96h-Acute	EC_{50} > 21.5 µg a.i./L	0.56 µg a.i./L	<0.1	NO
Saltwater fish (sheepshead minnow)	TGAI	96h-Acute	LC_{50} > 5.6 µg a.i./L		<0.1	
Saltwater algae (*Skeletonema*)	EP	96h-Acute	EC_{50} = 5 µg a.i./L		0.11	
Tier I Refined Drift Assessment: 6% drift from groundboom application						
Amphibians	TGAI	28d ELS	NOEC: 0.89 µg a.i./L, growth (High UV light)	0.18 µg a.i./L (E-1: 0.17 µg/L)	0.2	NO
	E-1	28d ELS	NOEC: 10 mg/L		<0.1	NO
Algae (*Selenastrum*)	TGAI	72h-Acute	EC_{50} = 0.16 µg a.i./L	0.034 µg a.i./L	0.2	NO
Tier I Refined Assessment for Runoff:						
Amphibians	TGAI	28d ELS	NOEC: 0.89 µg a.i./L, growth (High UV light)	1.2 µg a.i./L (E-1: 1.1 µg/L)	**1.3**	**YES**
	E-1	28d ELS	NOEC: 10 mg/L		<0.1	NO
Algae (*Selenastrum*)	TGAI	72h-Acute	EC_{50} = 0.16 µg a.i./L	0.43 µg a.i./L (E-1: 0.4ug/L)	**2.7**	**YES**
	E-1	72h-Acute	EC_{50} = 1.1 µg /L		0.36	NO

[1]E-1: major transformation product; [2] Corrected values are derived using the uncertainty factors in table 7-3; [3] EP: end-use product; [4] TGAI: technical grade active ingredient

Table 19 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Endpoints	Transformation Products Endpoints
Toxic or toxic equivalent as defined by the *Canadian Environmental Protection Act*[1]	Yes		Yes	Yes
Predominantly anthropogenic[2]	Yes		Yes	Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	Half-life: <1d	E-1:22d E-2: 7.7-10.3d E-3:154-495d
	Water	Half-life ≥ 182 days	Half-life: <1d	E-1: approximately 59d in whole system
	Sediment	Half-life ≥ 365 days	Half-life: <1d	N/A
	Air	Half-life ≥ 2 days or evidence of long range transport	Half-life or volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to	N/A

			occur based on the vapour pressure (4.3E-9 Pa at 20°C) and Henry's Law Constant (7.95E-10 atm m3/mole).	
Bioaccumulation[4]	Log $K_{OW} \geq 5$		3.4	E-3: 3.66 E-1 and E-2: < 3
	BCF ≥ 5000		18	N/A
	BAF ≥ 5000		N/A	N/A
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.	No, does not meet TSMP Track 1 criteria.

[1] All pesticides will be considered toxic or toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the toxicity criterion may be refined if required (in other words, all other TSMP criteria are met).

[2] The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.

[4] Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{OW}).

Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

The MRLs proposed for pyraflufen-ethyl in Canada are the same as corresponding tolerances established in the United States, except for livestock commodities, in accordance with Table 1, for which differences in MRLs/tolerances may be due to different livestock feed items and practices. American tolerances are listed in the Electronic Code of Federal Regulations, 40 CFR Part 180, by pesticide. Currently, there are no Codex MRLs[8] listed for pyraflufen-ethyl in or on any commodity on the Codex Alimentarius Pesticide Residues in Food website.

Table 1 compares the MRLs proposed for pyraflufen-ethyl in Canada with corresponding American tolerances.

Table 1 Comparison of Canadian MRLs, American Tolerances and Codex MRLs (where different)

Food Commodity	Canadian MRL (ppm)	American Tolerance (ppm)	Codex MRL (ppm)
Fat, meat and meat byproducts of cattle, goat, horse and sheep; Milk	0.02	0.03	Not Established
Eggs; Fat, meat and meat byproducts of hogs and poultry	0.02	Not Established	Not Established

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

Under the North American Free Trade Agreement (NAFTA), Canada, the United States and Mexico are committed to resolving MRL discrepancies to the broadest extent possible. Harmonization will standardize the protection of human health across North America and promote the free trade of safe food products. Until harmonization is achieved, the Canadian MRLs specified in this document are necessary. The differences in MRLs outlined above are not expected to impact businesses negatively or adversely affect international competitiveness of Canadian firms or to negatively affect any regions of Canada.

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[8] The Codex Alimentarius Commission is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	References
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2130073	1998, Method of analysis for impurities in technical grade, DACO: 2.13.1 CBI
2130074	1993, Validation of the analytical method of ET-751 technical, DACO: 2.13.1 CBI
2130075	2008, Validation of the analytical method for pyraflufen-ethyl technical, DACO: 2.13.1 CBI
2130076	2008, Validation of the analytical method for minor components in pyraflufen-ethyl technical, DACO: 2.13.1 CBI
2130077	2008, Validation of the analytical method for residual solvents in pyraflufen-ethyl technical, DACO: 2.13.1 CBI
2130079	1996, Identification of impurities presented in ET-751 technical, DACO: 2.13.2 CBI
2130080	2005, Analytical profile of five representative batches of pyraflufen-ethyl technical, DACO: 2.13.3 CBI
2130081	2007, Profile of five representative batches of pyraflufen-ethyl technical, DACO: 2.13.3 CBI
2130082	2000, ET-751: Determination of Physico-Chemical Properties of the Substance as Manufactured, DACO: 2.14.1,2.14.2,2.14.3,2.14.8 CBI
2130083	2000, Determination of dissociation constant for ET-751 technical, DACO: 2.14.10 CBI
2130084	1996, Measurement of IR, UV, NMR spectra of impurities presented in ET-751 technical, DACO: 2.14.12 CBI
2130086	1996, Absorption spectra (UV/VIS, IR, NMR, MS) of HME-Cl, DACO: 2.14.12 CBI
2130087	2000, Determination of stability to normal and elevated temperature and metals for ET-751 TGAI, DACO: 2.14.13 CBI
2130089	1997, Certificate of purity and stability of ET-751 technical, DACO: 2.14.14 CBI
2130090	2000, ET-751: Determination of Physico-Chemical Properties of Purified Active Substance, DACO: 2.14.11,2.14.12,2.14.2,2.14.4,2.14.5,2.14.6,2.14.7, 2.14.9 CBI
2130093	2000, Determination of density for ET-751, DACO: 2.14.6 CBI
2130094	1996, E1: Determination of the Solubility in Water Buffered at specified pH values, DACO: 2.14.7 CBI
2130095	1996, E1, E2, E3: Determination of Water Solubility and Octanol :Water Partition Coefficient, DACO: 2.14.7 CBI
2130096	1996, E1: Determination of the Vapour Pressure, DACO: 2.14.9 CBI
2130097	2000, Pyraflufen-ethyl (ET-751): Technical Active Ingredient (TGAI) and ET-51 2.5% EC (End Use Product), DACO: 2.11.1,2.11.2,2.11.3,2.11.4,2.3,2.4,2.5, 2.6,2.7,2.8,2.9 CBI

2220404 2007, (Pyraflufen-ethyl) ET-751: Technical Active Ingredient (TGAI) - Alternate Technical Source Product Properties, Group A-Product Identity, Composition and Analysis, DACO: 2.11.1,2.11.2,2.11.3,2.11.4 CBI

2220405 2007, Profile of Five Representative Batches of Pyraflufen-ethyl Technical, DACO: 2.13.1,2.13.2,2.13.3 CBI

2130246 2001, ET-751 2.5EC(N), DACO: 3.2.1,3.2.2,3.2.3 CBI

2130248 2002, Determination of pyraflufen-ethyl by HPLC analysis in formulation OS-159 2.5%EC(N) -Specificity-, DACO: 3.4.1 CBI

2130249 2005, Determination of the content of pyraflufen-ethyl in OS-159 2.5% EC(N), DACO: 3.4.1 CBI

2130250 2008, Pyraflufen-ethyl 2% SC and pyraflufen-ethyl 2.5% EC: validation of analytical procedures for determination of the active ingredient, DACO: 3.4.1 CBI

2130255 2006, Determination of appearance of OS-159 2.5% EC(N), DACO: 3.5.1 CBI

2130257 2005, OS-159 2.5% EC(N): Determination of the physical, chemical and technical properties of the plant protection product (emulsifiable concentrate), DACO: 3.5.1,3.5.2,3.5.3 CBI

2130258 2006, Determination of the accelerated storage stability of OS-159 2.5% EC(N) by heating (including determination of the active ingredient concentration, appearance, emulsifiability, emulsion-stability and re-emulsifiability and pH), DACO: 3.5.10 CBI

2130259 2007, Determination of the stability of OS-159 2.5%EC(N) over 2 years under ambient conditions (including determination of the active ingredient concentration, appearance, emulsifiability, emulsion-stability and re-emulsifiability and pH), DACO: 3.5.10 CB

2130260 2006, Determination of the flash-point of OS-159 2.5% EC(N), DACO: 3.5.11 CBI

2130261 2006, Statement on the explosive properties of OS-159 2.5% EC(N), DACO: 3.5.12 CBI

2130262 2006, Determination of miscibility for ET-751 2.5% EC, DACO: 3.5.13 CBI

2130263 2009, Corrosivity of Pyraflufen 2.5%EC, DACO: 3.5.14 CBI

2130264 2006, Determination of the density (liquid) of OS-159 2.5% EC(N), DACO: 3.5.6 CBI

2130265 2006, Determination of the pH of an aqueous dispersion of OS-159 2.5% EC(N), DACO: 3.5.7 CBI

2130266 2000, Determination of oxidizing or reducing action and chemical incompatibility for ET-751 2.5% EC, DACO: 3.5.8 CBI

2130267 2006, Determination of the viscosity of OS-159 2.5% EC(N), DACO: 3.5.9 CBI

2130147 1997, Validation of an analytical method for the determination of residues in soil, DACO: 8.2.2.1

2130148 2008, To conduct a validation of the analytical method pyraflufen E1/water/SJ/08/1 for the analysis of pyraflufen E1 in water, DACO: 8.2.2.3

2130149 1997, Analytical method validation of ET-751 and its metabolite E-1 in water, DACO: 8.2.2.3

2130150 2000, Analytical method of pyraflufen-ethyl in/on citrus raw agricultural commodities, DACO: 8.2.2.4

2130151	1997, Analytical method validation of ET-751 and its metabolite E-1 in wheat, DACO: 8.2.2.4
2130152	1995, Analytical method of ET-751 & its metabolite (E-1), DACO: 8.2.2.4
2130153	1998, Determination of pyraflufen-ethyl (ET-751) in cereal : validation of residue method, DACO: 8.2.2.4
2130154	1998, Analytical method for the determination of pyraflufen-ethyl (ET-751) in foodstuff of animal origin, DACO: 8.2.2.4
2130155	2000, Method validation for determination of pyraflufen-ethyl (ET-751) and its acid metabolite (E-1) in cotton RACs and processed cotton commodities and storage stability of these analytes in cotton RACs, DACO: 8.2.2.4

2.0 Human and Animal Health

2130070	2011, Comprehensive Data Summaries, DACO: 12.7,4.1,6.1,8.1,9.1
2130099	1995, Acute oral toxicity study of ET-751 technical in mice, DACO: 4.2.1
2130100	1995, Acute oral toxicity study of ET-751 technical in rat, DACO: 4.2.1
2130101	1995, Acute dermal toxicity study of ET-751 technical in rat, DACO: 4.2.2
2130102	1997, Histopathological examination for acute dermal toxicity study of ET-751 technical in rats (addendum to T-5018), DACO: 4.2.2
2130103	1995, Acute inhalation toxicity study of ET-751 technical in rat, DACO: 4.2.3
2130104	1995, Primary eye irritation study of ET-751 technical in rabbit, DACO: 4.2.4
2130105	1995, Primary dermal irritation study of ET-751 technical in rabbit, DACO: 4.2.5
2130107	1997, Delayed contact hypersensitivity study (incl. amendment no. 1), DACO: 4.2.6
2130108	2003, Research & Development Division, Nihon Nohyaku Co., Ltd., DACO: 4.2.9
2130110	1996, Toxicity study by dietary administration to CD rats for 13W followed by an 8W reversibility period, DACO: 4.3.1
2130112	1996, Toxicity study by oral (capsule) administration to beagle dogs for 13 weeks, DACO: 4.3.2
2130114	1996, Toxicity study by oral (capsule) administration to beagle dogs for 52W, DACO: 4.3.2
2130115	2000, 28-day dermal toxicity study with pyraflufen-ethyl technical in rats, DACO: 4.3.5
2130116	1998, Investigation of Liver Injury Caused by Dietary Administration of Pyraflufen-ethyl in Mice, DACO: 4.3.8
2130117	1996, ET-751: 78-week oral oncogenicity study in mice, DACO: 4.4.3
2130118	1997, Additional study of effect on proliferative activity of hepatic cells, DACO: 4.4.3
2130119	2000, ET-751: 78-week oral oncogenicity study in mice -Additional histochemical study on porphyrin accumulation in the liver, DACO: 4.4.3
2130120	1996, Combined oncogenicity and toxicity study by dietary administration for 104W, DACO: 4.4.1,4.4.2,4.4.4
2130121	2002, Combined oncogenicity and toxicity study by dietary administration for 104W - Supplement, DACO: 4.4.1,4.4.2,4.4.4
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2130123	1996, Two-generation reproduction study in rats, DACO: 4.5.1
2130124	2000, Two-generation reproduction study in rats - Amendment, DACO: 4.5.1
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2130126	1995, Preliminary teratology study following oral (gavage) administration in the rat, DACO: 4.5.2
2130128	1997, Preliminary teratology study following oral (gavage) administration in the rat, DACO: 4.5.3
2130129	1997, Assessment of mutagenic potential in amino-acid (Ames test), DACO: 4.5.4
2130130	1996, Report of reverse-mutation assay in bacteria, DACO: 4.5.4
2130131	1997, Mouse micronucleus test, DACO: 4.5.5
2130132	2006, Mouse micronucleus test - Attachment, DACO: 4.5.5
2130133	1997, Mouse lymphoma mutation assay, DACO: 4.5.6
2130134	1994, DNA repair test (rec-assay) with Bacillus subtilis, DACO: 4.5.7
2130135	1996, In vivo UDS test in rat hepatocytes, DACO: 4.5.8
2130136	1996, Absorption, distribution, metabolism & excretion of [pyrazole-5-14C]ET-751following a single oral administration to male & female rats, DACO: 4.5.9
2130137	1996, Metabolism & excretion of [pyrazole-5-14C] ET-751 into bile following a single oral administration to rats, DACO: 4.5.9
2130138	1996, Absorption, distribution, metabolism & excretion of a single oral dosing of [pyrazole-5-14C]ET-751 following repetitive oral dosing of non-radiolabeled test substance to rats, DACO: 4.5.9
2130139	1996, Metabolism & excretion of [phenyl-U-14C]ET-751 following single oral administration to male & female rats, DACO: 4.5.9
2130140	2011, Pyraflufen -ethyl Technical Grade: A 28-Day dietary immunotoxicity study in rats, DACO: 4.8(B)
2158736	1995, ET-751: Tolerance Study in the rabbit, DACO: 4.8
2158737	1994, ET-751: 78-week oncogenicity study in mice 28-day dose range finding study, DACO: 4.3.3
2158738	1994, ET-751: Preliminary toxicity study by oral (capsule) administration to beagle dogs, DACO: 4.3.8
2158739	1996, ET-751: Teratology Study in the rabbit, DACO: 4.5.3
2130240	2011, Comprehensive Data Summary, DACO: 10.1,12.7,3.1.1,3.1.2,3.1.3,3.1.4,4.1,5.1,6.1,7.1,8.1,9.1 CBI
2130268	1997, Acute oral toxicity test in the rat, DACO: 4.6.1
2130269	1997, Acute dermal toxicity (limit test) in the rat, DACO: 4.6.2
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2130271	1997, Primary eye irritation test in the rabbit, DACO: 4.6.4
2130272	2006, Primary skin irritation/corrosion study with OS-159 2.5%EC (N) in the rabbit (4-hour semi-occlusive application) (EU dossier attached), DACO: 4.6.5
2328724	1997, OS-159 2.5%EC(N): Buehler Delayed Contact Hypersensitivity Study in the Guinea Pig, DACO: 4.6.6
2328721	2013, Mode of Action Analysis: Pyraflufen-ethyl (ET-751)-Induced Hepatic Adenoma in Mice, DACO: 4.8
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2328719	2012, Pyraflufen-ethyl: Neurotoxicity study by a single oral gavage administration to Sprague-Dawley rats followed by a 14-day observation period, DACO: 4.5.12
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2130145	1999, A metabolism study with [14C]ET-751 on potato, DACO: 6.3
2130146	1999, A metabolism study with [14C]ET-751 on cotton, DACO: 6.3
2130150	2000, Analytical method of pyraflufen-ethyl in/on citrus raw agricultural commodities, DACO: 8.2.2.4
2130151	1997, Analytical method validation of ET-751 and its metabolite E-1 in wheat, DACO: 8.2.2.4
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2130153	1998, Determination of pyraflufen-ethyl (ET-751) in cereal : validation of residue method, DACO: 8.2.2.4
2130154	1998, Analytical method for the determination of pyraflufen-ethyl (ET-751) in foodstuff of animal origin, DACO: 8.2.2.4
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2130287	2008, Validation of multiresidue method DFG S 19 for the determination of residues of pyraflufen-ethyl and metabolite E-1 (pyraflufen) in cucumber, wheat (grain), orange and sunflower seed, DACO: 7.2.2
2130288	2000, Independent laboratory validation of analytical method for pyraflufen-ethyl and its metabolite (E-1) in/on apple, pear, grapes and oilseed rape, DACO: 7.2.3
2130291	1999, Independent laboratory validation for determination of pyraflufen-ethyl (ET-751) and its acid metabolite in rye matrices (A-5033), DACO: 7.2.3
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2130293	2008, Independent laboratory validation of analytical method for pyraflufen-ethyl and its metabolite (E-1) in/on apple, pear, grapes and oilseed rape, DACO: 7.2.3
2130294	2000, Independent laboratory validation (ILV) of analytical methods for the determination of pyraflufen-ethyl (ET-751) and its metabolite (E-1) in potato and cotton samples/matrices, DACO: 7.2.3
2130297	2002, Freezer storage stability of pyraflufen-ethyl and its acid metabolite E-1 in cereal samples, DACO: 7.3
2130298	2001, Storage stability of ET-751 and E-1 in corn, soybean and wheat, DACO: 7.3

2130300	2001, Magnitude of the residue of pyraflufen-ethyl in/on field corn following pre-plant application of ET-751, DACO: 7.4.1
2130301	2006, Magnitude of the residue of pyraflufen-ethyl and its metabolite in or on wheat raw agricultural and processed commodities following one preplant and one foliar application of ET herbicide/defoliant to spring wheat and one foliar application of ET herbicide/defoliant to spring wheat and one foliar application of ET herbicide/defoliant to winter wheat, DACO: 7.2.1,7.2.5,7.4.1,7.4.2
2130303	2006, Magnitude of the residue of pyraflufen-ethyl and its metabolite in or on field corn raw agricultural and processed commodities following one preplant and one foliar application of ET herbicide/defoliant, DACO: 7.2.1,7.4.1,7.4.2,7.4.5
2130304	2006, Magnitude of the residue of pyraflufen-ethyl and its metabolite in or on soybean raw agricultural and processed commodities following one preplant and one foliar application of ET herbicide/defoliant, DACO: 7.4.1,7.4.2,7.4.5
2130306	1998, Confined rotational crop study using radishes, lettuces and barley, DACO: 7.4.3
2130308	2001, Magnitude of the residue of pyraflufen-ethyl in/on soybean following pre-plant application of ET-751, DACO: 7.4.5
2130309	2006, Magnitude of ET-751 residues in bovine tissues and milk from a 28-day feeding study and radiovalidation in goat liver and milk, DACO: 7.5
2222169	2002, Magnitude of the Residue of Pyraflufen-ethyl in/on Wheat Following Pre-Plant Application of ET-751, DACO: 7.4.1,7.4.5
2222187	2001, Magnitude of the Residue of Pyraflufen-ethyl in/on Field Corn Following Pre-Plant Application of ET-751, DACO: 7.4.1,7.4.5
2222193	2000, Magnitude of the Residue of Pyraflufen-ethyl (ET-751) in/on Processed Fractions of Cotton Raw Agricultural Commodities, DACO: 7.4.5

3.0 Environment

2130156	1999, Hydrolysis of [14C]ET-751 at pH 5, 7 and 9, DACO: 8.2.3.2
2130157	1996, Aqueous hydrolysis study of ET-751, DACO: 8.2.3.2
2130160	1995, Soil degradation at 10, DACO: 8.2.3.3.1
2130161	1996, Photodegradation on a soil surface, DACO: 8.2.3.3.1
2130162	1996, Aqueous photolysis study using distilled water and river water, DACO: 8.2.3.3.2
2130163	1997, Aqueous photolysis study, DACO: 8.2.3.3.2
2130164	1996, Calculation of the quantum yield of ET-751, DACO: 8.2.3.3.2
2130165	1997, Soil degradation at 20, DACO: 8.2.3.4.2
2130166	1996, Soil degradation at 20, DACO: 8.2.3.4.2
2130167	1996, Aerobic Soil Metabolism, DACO: 8.2.3.4.2
2130168	1996, Aerobic Soil Metabolism, DACO: 8.2.3.4.2
2130169	1997, Aerobic soil metabolism, DACO: 8.2.3.4.2
2130170	2000, Aerobic soil metabolism of [14C]ET-751, DACO: 8.2.3.4.2
2130171	1995, Anaerobic Soil Metabolism, DACO: 8.2.3.4.4
2130172	1996, Anaerobic soil degradation at 20, DACO: 8.2.3.4.4
2130173	1996, Degradation & retention in water-sediment systems, DACO: 8.2.3.5.4
2130174	2000, Anaerobic aquatic metabolism of [14C]ET-751, DACO: 8.2.3.5.6

2130175	1996, Determination of Adsorption Coefficient on Soil (Koc) by HPLC Simulation, DACO: 8.2.4.2
2130176	1996, Adsorption/desorption in 3 soils, DACO: 8.2.4.2
2130177	1996, Adsorption/desorption in 3 soils - E2 Metabolite, DACO: 8.2.4.2
2130178	1996, Adsorption/desorption in 3 soils - E3 Metabolite, DACO: 8.2.4.2
2130179	1996, Soil column leaching of [Pyrazole-5-14C]ET-751 (normal study), DACO: 8.2.4.3.1
2130180	1996, Soil column leaching of [Pyrazole-5-14C]ET-751 (aged study), DACO: 8.2.4.3.2
2130181	1996, Acute toxicity on earthworms using an artificial soil test, DACO: 9.2.3.1
2130182	1996, Assessment of side effects to the Honey Bee in the laboratory, DACO: 9.2.4.1,9.2.4.2
2130184	1998, Effects of pyraflufen-ethyl (ET-751) on reproduction and growth of earthworms *Eisenia fetida* (savigny 1826) in artificial soil, DACO: 9.2.7
2130185	1996, Acute toxicity to daphnia magna - E1, DACO: 9.3.2
2130187	1996, Acute toxicity to daphnia magna, DACO: 9.3.2
2130188	1995, Acute toxicity to rainbow trout, DACO: 9.5.2.1
2130189	1996, E-1-Acute toxicity to rainbow trout, DACO: 9.5.2.1
2130190	1996, E-1-Acute toxicity to bluegill sunfish (Lepomis macrochirus), DACO: 9.5.2.2
2130191	1999, Determination of acute toxicity to bluegill sunfish (Lepomis macrochirus), DACO: 9.5.2.2
2130192	1995, Acute oral toxicity study in bobwhite quail with ET-751 technical, DACO: 9.6.2.1
2130193	1996, 5-day dietary toxicity study in bobwhite quail, DACO: 9.6.2.4
2130194	1996, 5-day dietary toxicity study in mallard duck, DACO: 9.6.2.5
2130195	2000, Reproduction study in bobwhite quail with pyraflufen-ethyl technical (by dietary admixture), DACO: 9.6.3.1
2130196	1997, Reproduction study in mallard duck by dietary admixture, DACO: 9.6.3.2
2130197	1996, Toxicity to the freshwater diatom *Navicula pelliculosa*, DACO: 9.8.2
2130198	1996, E-1-Toxicity to the freshwater diatom *Navicula pelliculosa*, DACO: 9.8.2
2130201	1997, Toxicity to the green alga (recovery), DACO: 9.8.2
2130202	1997, E-1-Toxicity to the green alga *Selenastrum capricornotum*, DACO: 9.8.2
2130203	2000, ET-751 2.5% EC-determination of effects of multiple applications on early seedling growth of ten plant species, DACO: 10.3.2(A)
2130204	2000, ET-751 2.5% EC-determination of effects on vegetative vigor of ten plant species, DACO: 10.3.2(A)
2130205	2000, ET-751 2.5% EC(N)-determination on effects on seedling emergence of ten plant species, DACO: 10.3.2(A)
2130206	1996, Toxicity to duckweed (Lemna gibba), DACO: 9.8.5
2130310	1999, Field soil dissipation of [pyrazole-14C] ET-751 in bare ground in Washington, DACO: 8.3.2
2130311	2002, Continuation of a Study of Soil Dissipation of (pyrazole-514C)ET-751 in Bare Ground in Washington to Obtain Analytical Date for Additional Soil Sampling Events, DACO: 8.3.2
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2130313 2000, Laboratory acute oral and contact toxicity test with the honeybee, *Apis mellifera*, DACO: 9.2.8

2130314 2006, Acute toxicity study in *Daphnia magna* with OS-159 2.5%EC(N) (static), DACO: 9.3.5

2130315 2000, Acute toxicity to water fleas, (*Daphnia magna*) under flow-through conditions. DACO: 9.3.5

2130316 2000, Acute toxicity to rainbow trout (*Oncorhynchus mykiss*) under flow through conditions, DACO: 9.5.4

2130318 2006, 96-hour acute toxicity study in rainbow trout with OS-159 2.5% EC(N) (static), DACO: 9.5.4

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2220409 2000, E-1 - Acute Toxicity to Mysids (*Mysidopsis bahia*) Under Static Conditions, DACO: 9.4.6

2220411 2000, E-1 - Acute Toxicity to Eastern Oysters (*Crassostrea virginica*) Under Static (Recirculated) Conditions, DACO: 9.4.6

2220413 2000, E-1 - Acute Toxicity to Sheepshead Minnow (*Cyprinodon variegatus*) Under Static Conditions, DACO: 9.5.4

2220415 1996, E-1: Chronic toxicity to fathead minnow (*Pimephales promelas*) embryos and larvae, DACO: 9.5.3.1

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2222197 2000, ET-751 2.5% EC(N): Acute Toxicity Test with the Parasitic Wasp, *Aphidius rhopalosiphi* (Hymenoptera: *Braconidae*), DACO: 9.2.8

2222198 2000, ET-751 2.5% EC(N) - Acute Toxicity to Bluegill Sunfish (*Lepomis macrochirus*) Under Flow-Through Conditions, DACO: 9.5.4

2222199 2000, ET-751 2.5% EC(N) - Acute Toxicity to the Freshwater Blue-Green Alga (*Anabaena flos-aquae*), DACO: 9.8.6

2222200 2000, ET-751 2.5% EC(N) - Acute Toxicity to the Freshwater Green Alga (*Pseudokirchneriella subcapitata*), DACO: 9.8.6

2222201 2000, ET-751 2.5% EC(N) - Acute Toxicity to the Marine Diatom, *Skeletonema costatum*, DACO: 9.8.6

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4.0 Value

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B. Additional Information Considered

i) Published Information

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